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Original Article

Comparative Study on the Corneal Endothelial Cell Count between Type 2 Diabetic and Non-Diabetic Patients

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ABSTRACT

Background: Diabetes mellitus is one of the commonest chronic disorders worldwide with a rapid rise in prevalence. In Iraq its prevalence is high especially in elderly age group. Patients with type 2 diabetes mellitus have higher vulnerability for complications, whether microvascular or macrovascular. Ocular complications are common in diabetes mellitus, and comprise diabetic retinopathy, diabetic papillopathy, cataract, glaucoma, dry eye disease and diabetic keratopathy. Diabetic keratopathy involves endothelial and epithelial tissues of the cornea, leading to persistent epithelial defect, corneal erosion, or corneal ulcers.

Aim of the Study: To compare the mean corneal endothelial cell count between patients with type 2 diabetes mellitus and non-diabetics.

Subjects and Methods: This is a case-control study conducted in Ibn Al Haitham Teaching Eye Hospital – Baghdad and included 249 participants, 125 cases with type 2 diabetes and 124 controls who had no diabetes. Endothelial cell count was measured for 1 eye of each participant using TOPCON® SP-3000P microscope. Patients who had diabetes for less than 5 years, and patients who had previous ocular surgery, injury or disorders were excluded.

Results: There was a significant difference in endothelial cell count between cases with type 2 diabetes mellitus and controls; $P = 0.001$. There was also a significant negative correlation between age and endothelial cell count, $R = -0.20$, $P = 0.002$. Similarly, there was a significant negative correlation between duration of diabetes mellitus and endothelial cell count, $R = -0.44$, $P < 0.001$.

Conclusions: Type 2 diabetes mellitus causes significant reduction in mean corneal endothelial cell count. There is also a negative correlation between corneal endothelial cell count and both age and duration of the disease.

Introduction

Diabetes mellitus (DM) is one of the commonest chronic metabolic disorders, leading to a global public health burden of disease. This rapid rise in prevalence is attributed to several factors including aging, population growth, obesity and lack of physical activity.[1] Iraq, among the Middle-Eastern countries, has a high prevalence of DM among its population, especially in elderly age group, with a prevalence of 15% in people of age 50 years and older,

as estimated by the Iraqi Ministry of Health (MOH) in its report of Iraq Family Health Survey (IFHS) conducted on 2006 and 2007 in collaboration with the World Health Organization (WHO).[2]

Three types of DM have been described: Type 1 or insulin dependent DM (IDDM), type 2 or non-insulin dependent DM (NIDDM), and gestational DM (GDM).[3] Patients with type 2 DM have higher vulnerability for complications, both short-term and long-term, when compared to type 1 diabetics. This is partly related to the higher prevalence of this type of DM as well as its later recognition when compared to type 1 DM. [4] These complications, whether microvascular complications such as retinopathy and nephropathy, or macrovascular complications such as stroke and peripheral arterial diseases, make DM an important and challenging health issue of the 21st century.[5]

Ocular complications are common, involving various tissues of the eye and comprise diabetic retinopathy, diabetic papillopathy, cataract, glaucoma, dry eye disease and diabetic keratopathy. [6, 7]

The cornea is the transparent anterior structure of the eye that covers and protects the iris, pupil, and anterior chamber.[8] The corneal endothelium is a monolayer of cells lining the posterior surface of the cornea. This layer has an important role in hydration control of the stroma and maintaining stromal deturgescence by an active pump action that draws fluid from the stroma into the aqueous humor. [9, 10]

Endothelial cell density of human cornea varies throughout life, with an approximate 6000 cells/mm2 at birth, declining to approximately 3500 cells/mm2 at age of 5 years. This decline is attributed to both growth of the cornea and to the decrease in the number of endothelial cells.[10] It is estimated that the average rate at which the endothelial cell density declines annually is about 0.6% per year.[11] Correspondingly it was found that mean cell density declined from 3400 cells/mm2 at age 15 years to about 2300 cells/mm2 at age of 85 years.[10]

Diabetic keratopathy is a common ocular complication of DM involving endothelial and epithelial tissues of the cornea, leading to persistent epithelial defect, corneal erosion, or corneal ulcers.[12] Diabetic keratopathy causes alterations to these corneal tissues that lead to 3 main distinct types of tissue dysfunction: impaired wound healing of the corneal epithelium, sub-basal nerves abnormalities, and inadequate pump function of the corneal endothelium.[9] These changes result in thickening of the endothelium, decreased corneal sensitivity, and tear secretion abnormalities.[13]

The structure and function of the corneal endothelium can be assessed using non-contact specular microscopy, which is a non-invasive technique that provides morphological analysis of the corneal endothelial cell layer.[14].

Aim of the Study

To compare the mean corneal endothelial cell count between patients with type 2 diabetes mellitus and non-diabetics using specular microscope.

Subjects and Methods

This is a case-control study conducted in Ibn Al Haitham Teaching Eye Hospital - Baghdad from July 2017 through April 2018 and included a total of 249 participants, 125 cases with type 2 diabetes diagnosed by physician their age range 40-70 years (57.2 ± 8.5), and 124 control who had no diabetes according to fasting blood sugar their age range 40-70 years (56.1 ± 9.2).

Formal permission and approval were obtained from related offices to conduct this study. Verbal Informed consent was obtained from all participants after explaining the purpose of the study and type of data collected, and data was treated in anonymity and confidentiality.

Information obtained from participants included age, gender, history of diabetes and other chronic disorders, and detailed history of any previous ocular disorders or interventions. All study participant underwent specular microscopy for one eye to measure the endothelial cell count. This was done using TOPCON® SP-3000P (Japan) non-contact specular microscope by the same operator. Images undergoing analysis involved about 100±20 endothelial cells from the center of the cornea. This procedure was repeated three times for each eye, and the median number of endothelial cell density was selected. Examinations for anterior and posterior segments were performed before specular microscopy by slit-lamp biomicroscopy including intraocular pressure measurement by Goldmann applanation tonometer and air puff tonometers.

Exclusion criteria were patients who had diabetes for less than 5 years from the date of diagnosis, patients with eye trauma or previous surgery to the eye, patients who wear contact lenses, uveitis or other ocular infections, and patients who had previously undergone corrective laser eye surgery, previous retinal photocoagulation, glaucoma, dry eye, pseudo-exfoliation, pigment dispersion syndrome, endothelial corneal dystrophy, topical medication and smoking.

Statistical Analysis

Statistical Package for Social Sciences (SPSS®) Software version 23.0 for Linux® has been used to perform statistical analysis in this study. Qualitative data are presented as number and percentage, while continuous numerical data are presented as mean ± standard deviation. Comparison of study groups was carried out using Student's t-test for continuous data, and continuous variables were compared using Pearson's product-moment correlation coefficient, and plotted on scatter diagrams to further illustrate the relationship between the two variables. P-value of < 0.05 is considered statistically significant.

Results

The study included 249 participants, 125 cases of DM type 2 and 124 controls. No significant difference exists in age between cases and controls, as detailed in table (1), thus eliminating the effect of age as a confounder. Age groups of study participants were illustrated in figure (1).

Table 1: Age distribution of study participants

Age (years)	Cases (n=125)	Controls (n=124)
Range	40 – 70	40 – 70
Mean ± SD	57.2 ± 8.5	56.1 ± 9.2

Age (years)	Cases (n=125)	Controls (n=124)
Student's t-test = 1.00, d.f.* = 247, P-value = 0.319		

* d.f. = degrees of freedom

To compare between studies groups regarding endothelial cell count; independent-samples t-test was used. There was a statistically significant difference in endothelial cell count between cases group and control group; t (247) = -3.41, P = 0.001, as detailed in table (2). Table (2)

Table 2: Comparison of endothelial cell count between cases and controls

Parameter	**Cases (n=125)**	**Controls (n=124)**
Mean	2543.65	2647.10
SD	256.51	220.27
Student's t = -3.41. , d.f. = 247, P = 0.001		

A Pearson product-moment correlation coefficient was computed to assess the relationship between age and endothelial cell count. There was a significant negative correlation between the two variables, coefficient of correlation (R) = -0.20, coefficient of determination (R2) = 0.04, n = 249, P-value = 0.002. A scatterplot summarizes the results (Figure 1).

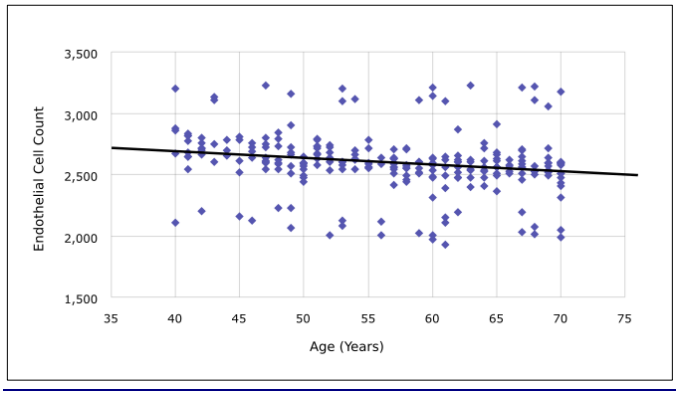

Figure.1: Scatterplot diagram showing correlation between endothelial cell count and age in years**Table 3:** Distribution according to maternal age with comparison significance.

Another comparison was performed between endothelial cell count and duration of DM using Pearson's product-moment correlation coefficient. There was also a highly significant negative correlation between the two variables, coefficient of correlation (R) = -0.44, coefficient of determination (R2) = 0.19, n = 249, P < 0.001, as illustrated in figure (2).

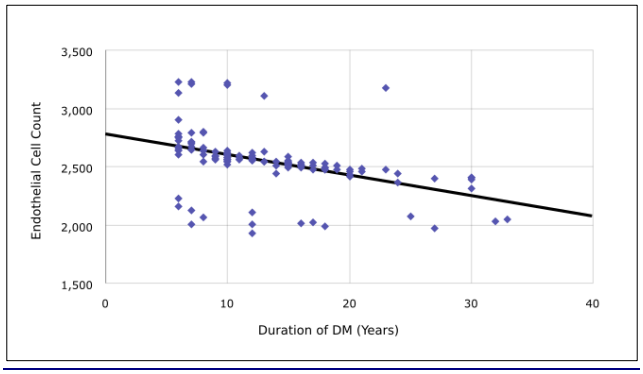

Figure.2: Scatterplot diagram showing correlation between endothelial cell count and duration of DM in years.

Linear regression was calculated between endothelial cell count and diabetes with adjustment to age and gender, to predict endothelial cell count based on presence of diabetes. A significant regression equation was found (P-value < 0.001), with a coefficient of determination (R2) of 0.08. Endothelial cell count is lower by an average of 98 cells in diabetic patients when compared with non-diabetics, regardless of age and gender (adjusted t-test=-3.27, P-value = 0.001).

Discussion

In this study, the study groups were first compared regarding difference in age and gender, and no significant difference was observed, therefore reducing the confounder effect of those two characteristics. Comparison of the study groups regarding endothelial cell count have shown a statistically significant reduction of 3.91% in mean endothelial cell count between cases and controls (P = 0.001). This finding is consistent with a similar study conducted in Japan by Inoue et al. which found a significant reduction of 4.08% in mean endothelial cell count (P = 0.016).[15] Another study conducted in Malaysia by Choo et al. have found a significant reduction of 4.5% in mean endothelial cell count.[16] Similarly, El-Agamy et al. found a reduction of 5.24% among Saudi Arabian patients who were enrolled in that study[17], and Lee et al. found a reduction of 4.54% in their Korean study.[18] A lower, yet still significant, reduction of 2.82% was observed by Ahuja et al. in their study done in India.[19] However, the results of the study in Denmark by Storr-Paulsen et al. have shown non-significant reduction of only 1.03% in mean endothelial count, which is not consistent with the findings in the present study.[20]

This marked change in the diabetic corneal tissue could be explained by the effect of DM on the activity of Na+-K+ ATPase enzyme, elevated glucose level reduces the activity of the aforementioned enzyme, changing the permeability and morphology of the cornea, which in turn leads to the destruction of the corneal cells. Diabetes also slows down Krebs cycle in the cornea, therefore the production of ATP is reduced. This reduction affects the endothelial pump function, further damaging the cornea. [16, 17]

Analysis of Pearson correlation between endothelial cell count and age have shown a significant correlation indicating that endothelial cell count decreases with increasing age. This reduction over time could be part of certain morphological changes that occur with aging process. Similar finding was reported by Busted et al.

[21] and Parekh et al. [22] However, Inoue et al. reported no significant correlation with age.[15]

This study demonstrated a significant negative correlation between duration of DM and endothelial cell count, meaning that increases in duration of DM were correlated to decreases in endothelial cell count. A similar significant correlation was reported by Parekh et al. [22] But El-Agamy et al. found no such correlation.[17]

A possible limitation of this study is the potential of presence of confounding factors that influence the association between variables under study, although adjustment to age and gender used in this study significantly reduced the confounding effect of those two variables.

The results and findings in this study concludes that mean corneal endothelial cell count is significantly lower in patients with type 2 diabetes mellitus when compared to non-diabetics.

The results also described that there is significant correlation between age and mean corneal endothelial cell count, suggesting that mean corneal endothelial cell count decreases with aging.

Another conclusion is the demonstration of the correlation between the duration of DM and the mean corneal endothelial cell count, showing that longer the duration of disease, lead to lower mean corneal endothelial cell count.

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