Int Ophthalmol (2019) 39:1735–1741
https://doi.org/10.1007/s10792-018-0995-y

ORIGINAL PAPER

Endothelial cell density changes in diabetic and nondiabetic eyes undergoing phacoemulsification employing phaco-chop technique

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Received: 1 November 2017 / Accepted: 21 July 2018 / Published online: 28 July 2018

Abstract

Purpose To assess endothelial cell density (ECD) changes on diabetic and nondiabetic patients after phacoemulsification surgery employing the phaco-chop technique.

Methods This is a prospective, experimental and comparative study. We included type-two diabetic (T2DM) patients and nondiabetic patients who underwent phacoemulsification performed by a single surgeon employing the horizontal phaco-chop technique. ECD and central corneal thickness (CCT), the coefficient of variation and percentage of polymegathism were measured and compared. Specular microscopy was used to evaluate the number of endothelial cells in patients during surgical pre-assessment and at the 1- and 3-month follow-up visits.

Results A total of 42 eyes from 42 patients were included: 21 eyes in the T2DM group and 21 eyes in the nondiabetic group. No statistically significant differences were found between groups in terms of age and sex distribution ($p = 0.296$; $p = 0.502$, respectively). Mean postoperative (at 1 and 3-month follow-up) endothelial cell count of the T2DM group was not significantly lower than the nondiabetic group ($p = 0.341$ and $p = 0.065$, respectively). Postoperative CCT measurements demonstrated no significant variations between groups, showing a mean 557.8 ± 48.0 and 543.3 ± 41.0 μm, respectively ($p = 0.472$). Nonetheless, significant differences were evidenced for CoV values for both the pre-surgical and the postoperative follow-up visits between groups, as well as ECD values inside each group.

Conclusions The present study reveals significant differences between pre-surgical and postoperative mean ECD values; however, no statistically significant differences were found when comparing ECD at each follow-up visit between diabetic patients without evidence of high-risk proliferative diabetic retinopathy and nondiabetic patients undergoing phacoemulsification employing phaco-chop technique.

Keywords Cataract surgery · Phacoemulsification · Endothelial cell density · Type-two diabetes · Corneal endothelium

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Introduction

The corneal endothelium is a key factor for maintaining a normal thickness, hydration and transparent corneal tissue [1]. It consists of a single hexagonalshaped cell layer with no in vivo mitotic capability [2]. For that reason, a significant change in the endothelial cells count is compensated mostly, through expansion and cell mobilization [3]. However, several conditions affect the corneal endothelium, such as age, contact lens use, ocular trauma, diabetes mellitus and mechanical manipulation [2, 4].

Phacoemulsification is the most frequently performed ophthalmic surgery around the world, and today it focuses on rapid visual rehabilitation [5]; however, regardless of constant improvements in surgical techniques, corneal endothelial decrease after cataract surgery remains to be a topic of concern in patients with dysfunctional endothelium [6]. Diabetes can affect both the corneal thickness and the corneal endothelium; hyperglycemia alone can lead to endothelial alterations that can convert a routine surgery into a high-risk surgical case [7].

Several studies have addressed corneal endothelium dysfunction in type-two diabetes mellitus; however, few publications have demonstrated the rate of the endothelial cell count changes after phacoemulsification using different surgical techniques in diabetic patients in comparison with matched nondiabetic controls in controlled conditions.

The purpose of the present study was to assess the differences in the corneal endothelial count and the central corneal thickness between type-two diabetic (T2DM) and nondiabetic patients undergoing phacoemulsification surgery employing horizontal phaco-chop technique.

Methods

The Internal Review Board of the Asociación para Evitar la Ceguera approved this study. All the procedures conformed to the tenets of the Declaration of Helsinki. A written informed consent form was obtained from all of the participants after an explanation of the procedures to be used and possible complications.

Study design

This is a prospective, experimental and comparative study, conducted at the Anterior Segment Surgery Department at the Asociación para Evitar la Ceguera; México city, Mexico.

Patients

Key inclusion criteria included adult patients from 50 to 80 years of age, diagnosed with type-2 diabetes mellitus (T2DM) in concordance with the WHO criteria [8], diagnosed in the previous 5 years and in glycemic control evidenced by HbA1c values of 48 mmol/mol (6.5%) with no prior ocular disease, healthy corneas and grade 2 cataracts according to the Lens Opacities Classification System II (LOCS II), NO2NC2 to NO3NC3 [9] undergoing routine phacoemulsification surgery using horizontal phaco-chop technique without complications. The control group consisted of nondiabetic patients diagnosed with NO2NC2 to NO3NC3 cataracts with no significant age and gender distribution differences. We excluded patients with evidence of high-risk proliferative diabetic retinopathy (T2DM group), characterized by the occurrence of vitreous hemorrhage or tractional retinal detachment; any type of corneal pathology, preoperative endothelial count < 1500 cells/mm, contact lens wear history, ocular trauma or surgery, current use of any kind of ocular treatment other than eye lubricant, and patients with conditions that would prevent evaluation of the cornea by specular microscopy.

All of the subjects had a comprehensive ocular examination including a review of the medical history, slit-lamp examination of the anterior segment, where cataracts were graded according to LOCS II [9]. In addition, diabetic retinopathy classification was obtained according to the Early Treatment Diabetic Retinopathy Study (ETDRS) standardization protocols [10].

Outcome measures

The specular microscopy examination and corneal topography were performed before surgery, at the 1- and 3-month follow-up visits after the phacoemulsification procedure. Specular microscopy was determined by SP-2000P specular noncontact (Topcon America Corporation, Paramus, NJ) microscope, and the endothelial cell density (cells/mm^2) was calculated by analyzing 30 cells of the central cornea before surgery and after subsequent monitoring operation according to protocol. In addition, central corneal thickness (CCT), coefficient of variation (CoV) and percentage of polymegathism were obtained. Three repeated measurements obtained by a single physician

(RZO) were utilized for each examination. Both, the physician and surgeon were blinded to each patients group.

Surgical technique

All patients underwent phacoemulsification surgery with an in-the-bag single-piece intraocular lens implant, without complications. All eyes were dilated using two drops of tropicamide/phenylephrine 1 h before the surgical procedure. The same surgeon (E.F.M.) performed all the surgical procedures employing the Infiniti® Vision System and a 0.9-mm ABS Mini-Flared 45° Kelman tip (Novartis Laboratories, Basel, Switzerland). In addition, a standard technique of horizontal-chop under topical anesthesia was performed, using one drop of tetracaine hydrochloride ophthalmic solution 0.5% (Ponti Ofteno® Sophia Laboratories, Guadalajara, Mexico) five times on hour before surgery. A 2.4 mm clear corneal incisions and manually created capsulorhexes from 5.0 to 5.5 mm were performed for all surgeries, using the same ophthalmic viscosurgical device (OVD) Duovisc® (3.0% sodium hyaluronate, 4.0% chondroitin sulfate with 1.0% sodium hyaluronate Novartis Laboratory Basel, Switzerland). Fluid parameters for the two surgical configurations were set as follows: vacuum limit 350, aspiration flow rate of 40 mL/min. US parameters were set at 20% linear power with 50% of torsional amplitude. After cataract removal and aspiration of cortical material, the appropriate IOL was implanted in the capsular bag and the procedure was concluded. Finally, all patients received combined tobramycin/dexamethasone eye drops BID, as postoperative treatment.

Statistical analysis

A sample size of 42 subjects, 21 per group was determined sufficient to compare means of two samples, with a two-tailed α of 0.05, a β of 0.2, an SD of 1.15 and 80% test power.

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software (version 15, SPSS, Inc., Chicago, IL, USA) and Prism GraphPad software (Prism Inc. version 6.0) was employed for correlation Graphs. Continuous variables are displayed as mean ± standard deviation (SD) and percentages, respectively. Differences between means of continuous variables were assessed using a paired *t* test for normally distributed data, whereas the Wilcoxon test was applied to non-normal distributed data. An ordinary one-way ANOVA was utilized to detect statistically significant differences among endothelial cell density measurements. In addition, the Pearson's correlation coefficient (r) and linear regression analyses were obtained between age and endothelial cell loss. A p value < 0.05 was considered to be statistically significant. Gaussian distribution was determined using the D'Agostino–Pearson omnibus normality test for all variables.

Results

A total of 42 eyes from 42 patients were included in this study. Twenty-one eyes in the T2DM group, diagnosed with mild-to-moderate diabetic retinopathy and 21 eyes in the control group (nondiabetic patients), both groups with grade 2 cataracts according to LOCS II (NO2NC2 to NO3NC3).

The overall mean age found was 67.09 ± 9.88. The two groups were similar in terms of age and sex distribution, and no statistically significant differences were found ($p = 0.296$; $p = 0.502$, respectively).

Pre-surgical and postoperative measurements (at the 1- and the 3-month follow-up visits) for ECD, CCT, CoV and polymegathism between groups are summarized in Table 1.

Mean preoperative endothelial cell density was not significantly different between groups (2249 ± 408.7 and 2173 ± 435.9, respectively; $p = 0.417$). However, significant differences were evidenced when comparing the mean ECD values at the pre-surgical, 1- and 3-month follow-up visits for each group ($p < 0.0001$ and $p = 0.002$, respectively), as depicted in Fig. 1.

No statistically significant differences were found when comparing ECD at the pre-surgical, 1- and 3-month follow-up visits between groups ($p = 0.417$, $p = 0.341$ and $p = 0.065$, respectively), as shown in Fig. 2.

A significant correlation was observed between age and the absolute endothelial cell loss (ECL) for the T2DM group at the 3-month follow-up visit ($r = 0.449$; $R^2 = 0.201$; $p = 0.047$). Conversely, such correlation was not observed in nondiabetic patients

Table 1 Pre-surgical and postoperative values for ECD, CCT, CoV and polymegathism between groups

Parameter	T2DM (ECD)	Nondiabetic (ECD)	**p* value
Pre-surgical ECD (cells/mm^2)	2249 ± 408.7	2173 ± 435.9	0.417
1-month postoperative ECD (cells/mm^2)	1760 ± 414.6	1895 ± 468.1	0.341
3-month postoperative ECD (cells/mm^2)	1595 ± 403.2	1875 ± 443.2	0.065
Pre-surgical CCT (μm)	571.6 ± 48.3	559.7 ± 41.1	0.379
1-month postoperative CCT (μm)	557.8 ± 48.0	543.3 ± 41.0	0.472
3-month postoperative CCT (μm)	565.2 ± 47.2	556.1 ± 40.3	0.443
Pre-surgical CoV	48.1 ± 3.81	40.0 ± 3.42	0.001
CoV at the 1-month visit	54.12 ± 4.6	45.42 ± 7.2	0.002
CoV at the 3-month visit	55.40 ± 5.4	46.44 ± 8.1	0.030
Percentage of polymegathism at the 1-month visit	51.03	44.01	0.062
Percentage of polymegathism at the 3-month visit	50.51	46.21	0.044

ECD Endothelial cell density (expressed in mean ± standard deviation), *CCT* central corneal thickness, *T2DM* type-two diabetes mellitus and *CoV* coefficient of variation

*Paired *t* test was performed to detect statistically significant differences between groups

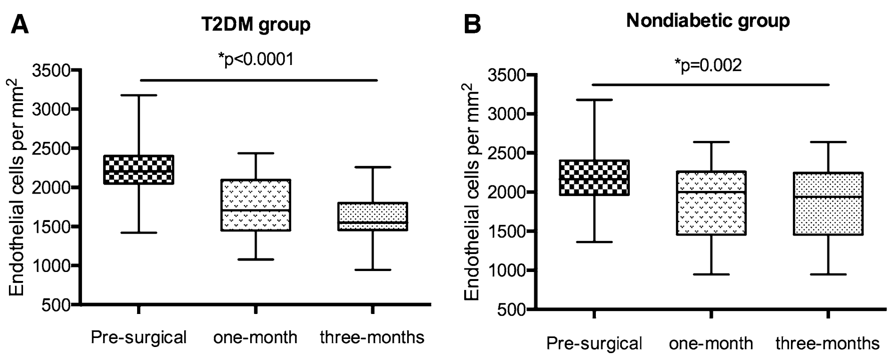


Fig. 1 **a** Comparison of ECD measurements among the pre-surgical, 1- and 3-month follow-up visits for the T2DM group. **b** Nondiabetic patients group. *Ordinary one-way ANOVA test

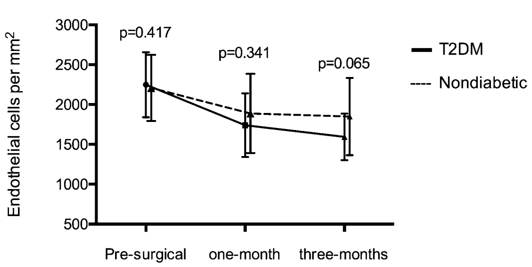


Fig. 2 Comparison of mean ECD between groups at the pre-surgical, 1- and 3-month follow-up visits. *Paired *t* test

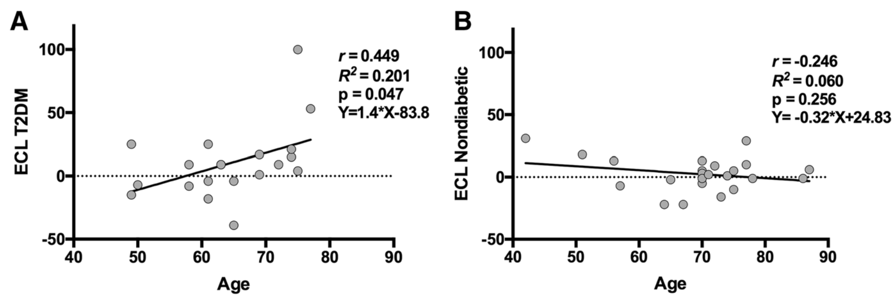
($r = 0.246$; $R^2 = 0.060$; $p = 0.256$), as depicted in Fig. 3.

The central cornea had a similar thickness in the T2DM group when compared to the control group (nondiabetic patients). No statistically significant differences were evidenced in CCT measurements before the surgical procedure showing a mean 571.6 ± 48.3 and 559.7 ± 41.1 μm, respectively ($p = 0.379$). Similarly, CCT measurements at the 1-month follow-up visit demonstrated no significant variations between groups, showing a mean 557.8 ± 48.0 and 543.3 ± 41.0 μm, respectively ($p = 0.472$), as depicted in Fig. 4.

Discussion

Eyes of T2DM patients are subject to various metabolic changes due to hyperglycemia. Corneal endothelium has shown morphological and morphometric alterations manifested by pleomorphism and polymegathism, as well as a lower percentage of hexagonal cells [1–3]. Di Mattio et al. [2] reported a

Fig. 3 Pearson correlation coefficient and linear regression analysis obtained between age and absolute endothelial cell loss (ECL) for **a** T2DM group and **b** nondiabetic group



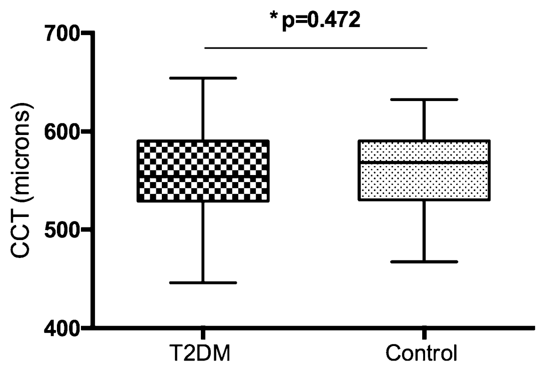


Fig. 4 Post-surgical central corneal thickness measurements between groups at the 1-month follow-up visit. *Paired *t* test

decrease in active transport of ascorbic acid, which is an extremely important antioxidant factor in cellular metabolism in ocular tissues, through the endothelial cells of diabetic patients. These biochemical and physiological alterations have been attributed to changes in the shape, size and cellular density, which reduce the number of functioning pumps [1–4]. Regarding studies on endothelial density, Siribunkum et al. [4] reported a higher count with decreasing cell size. Inoue and Kato [5] assert in their study that there is a lower endothelial density without affecting corneal thickness in diabetic patients after phacoemulsification.

Currently, a large number of patients undergo phacoemulsification cataract surgery every year, and this procedure has been associated with various reports of significant decrease in endothelial cells in both the short term and long term [6]. In this regard, it has been reported an endothelial cell loss of 0.9% per year after phacoemulsification surgery in nondiabetic patients [7], nonetheless, is also reported even more severe endothelial depletion after phacoemulsification of hard cataracts [11].

Some authors have studied corneal endothelium following phacoemulsification in diabetic and nondiabetic patients. For example, Goebbels et al. [12] reported in his fluorometry studies no endothelial permeability differences between diabetic and nondiabetic patients after phacoemulsification. Moreover, Inoue and Tokuda [13] studied the factors that predispose to endothelial cell count decrement following phacoemulsification, finding that the presence of diabetes does not influence the decrease in endothelial density, with age being the only predisposing factor. On the other hand, Hugo et al. [14] reported that, although in their study they evidenced a greater decrease in endothelial cells in well-controlled diabetic patients following phacoemulsification, this decrease did not affect corneal function or alter central corneal thickness. In addition, Misra et al. concluded that despite finding a decrease in the corneal subnasal nerve plexus in diabetic patients following phacoemulsification, there is no predisposition to greater endothelial cell count changes in nondiabetic patients [15].

Most studies in the literature confirm that the corneal endothelium of the diabetic patient presents morphological alterations; however, it remains controversial if phacoemulsification produces a greater alteration in the postoperative endothelial cell count and corneal thickness in diabetic patients than in nondiabetic patients. The majority of studies agree that in poorly controlled diabetic patients there are qualitative and quantitative alterations at the corneal level [16]. However, a detailed assessment of endothelial cell count according to specific phacoemulsification-technique employed and parameters used on patients controlled for the degree of nuclear density is essential to accurately evaluate the influence of surgical technique on diabetic patients' outcome.

In our study, significant differences in mean ECD values between pre-surgical and postoperative (1- and 3-month follow-up visits) were evidenced within each group independently; this could be partially attributable to endothelial cell loss induced by the surgical procedure; however, no statistically significant differences were found when comparing ECD at each measurement point between groups. Therefore, no significant changes were demonstrated between ECD values between diabetic patients and nondiabetic patients undergoing phacoemulsification employing phaco-chop technique.

In addition, it is important to highlight the significant differences evidenced on the CoV between groups in both the pre-surgical and the postoperative follow-up visits since morphological and functional anomalies have been observed in the corneal endothelium of diabetic patients when compared with corneas of healthy subjects [12–16]. These anomalies include changes in cell density, percentage of cells, hexagonality, and variation coefficient [16]. In addition to these findings, hardly any variation in the postoperative corneal pachymetry measurements 1 month after surgery were evidenced between groups, where non-significant differences were encountered for central corneal thickness.

It is also notable to underscore the fact that diabetic patients lost more endothelial cells progressively from the 1-month post-surgical visit to the 3-month follow-up consultation than their nondiabetic counterparts, which remained stationary. Also, the cell loss significantly correlated with age in diabetic patients, whereas this correlation was not evident in nondiabetic patients. Nonetheless, considering that the post-op CCT is not different between groups, it may suggest that despite losing more cells and having higher CoV, the endothelium of diabetic patients is still able to function normally.

The employment of horizontal phaco-chop technique has been widely assessed for cataract surgery, and several studies report no differences when compared to other phacoemulsification techniques; however, in a recent report by Park et al., the phaco-chop technique can be more effective for lens removal, with less corneal endothelial damage, than the divide-and-conquer and stop-and-chop techniques in eyes with hard cataract having coaxial phacoemulsification surgery [17].

Several limitations in this study should be noted, and one of the main weaknesses of this study is the low sample size; however, our sample size calculation was determined sufficient to compare means of two samples, with a two-tailed α of 0.05, a β of 0.2 and 80% test power. Another limitation is the short-term follow-up of the studied population. Nonetheless, we estimate that postoperative endothelial cell count and corneal thickness measurements within 3 months after the phacoemulsification procedure are sufficient to portray an accurate depiction of the final outcome.

In conclusion, despite good glycemic control and no corneal abnormalities before surgery, the endothelium in diabetic subjects is more vulnerable to surgical trauma. However, taking these factors into account may contribute to improve the surgical outcome for diabetic patients, especially employing efficient surgical phacoemulsification techniques like the phaco-chop technique. A major finding of our manuscript is that despite the lower densities observed postoperatively on the T2DM group, no statistically significant differences on postoperative ECD are found when employing phaco-chop technique between diabetic patients without evidence of high-risk proliferative diabetic retinopathy and control nondiabetic patients undergoing routine phacoemulsification, at the 1- and 3-month follow-up visits. Nonetheless, the endothelial cell loss significantly correlated with age in diabetic patients, whereas this correlation was not evident in nondiabetic patients.

Acknowledgements We would like to thank all patients that contributed their time and thus allowed us to obtain the data for this publication. Our deepest appreciation to the Luis Sánchez Bulnes Hospital, Asociación para Evitar la Ceguera.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria, educational grants, participation in speakers' bureaus, membership, employment, consultancies, stock ownership or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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