Impact of Donor, Host, and Surgical Parameters on High Endothelial Cell Density More Than 5 Years after Penetrating Keratoplasty

Einfluss von Spender-, Empfänger- und chirurgischen Parametern auf die hohe Endothelzelldichte mehr als 5 Jahre nach perforierender Keratoplastik

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ABSTRACT

Objectives To investigate the correlation between postoperative endothelial cell loss (ECL) and donor, host, and surgical parameters, and to assess the clinical impact of maintaining a high endothelial cell density (ECD) of ≥ 1500 cells/mm^2 5 years after penetrating keratoplasty (PKP).

Methods This retrospective cohort study included 216 eyes with 5 years of follow-up, of which 94 had annual visits, and who underwent normal-risk elective PKP for noninfectious indications by one corneal microsurgeon (B. S.) between 2009 and 2016.

Results Among the 216 eyes, ECL (39.1 %) over 5 years postoperative exhibited weak positive correlations with storage solution time ($p = 0.024$) and postmortem time ($p = 0.028$), and moderately positively correlations with the preoperative ECD ($p < 0.001$). The 5-year postoperative ECL differed significantly between in domo-prepared (36.8 %) and ex domo donor corneas (46.3 %; $p = 0.001$). In the 94 eyes, no significant differences were found between the two groups for central pupil pachymetry (CCT) and BCVA ($p > 0.074$). However, CCT increased significantly between 1 and 4 years ($p = 0.034$) and 1 and 5 years postoperatively ($p = 0.012$), respectively. BCVA improved significantly at 1 year postoperatively and continued to improve until 2 years postoperatively ($p < 0.001$).

Conclusion The Lions corneal bank Saar-Lor-Lux achieved a significantly reduced ECL (36.8 %) over 5 years compared to ex domo donor corneas (46.3 %). A weak positive correlation was found between ECL with the storage solution time and the postmortem time, as well as a moderate positive correlation with the preoperative ECD. Although CCT increased significantly over 5 years, BCVA improved significantly from the first to the second postoperative year and remained stable thereafter.

ZUSAMMENFASSUNG

Zielsetzung Untersuchung der Korrelation zwischen postoperativem Endothelzellverlust (ECL) und Spender-, Empfänger- und chirurgischen Parametern sowie Bewertung der klinischen Auswirkungen der Erhaltung einer hohen Endothelzelldichte (ECD) von ≥ 1500 Zellen/mm^2 5 Jahre nach penetrierender Keratoplastik (PKP).

Methoden Diese retrospektive Kohortenstudie umfasste 216 Augen mit einer Nachbeobachtungszeit von 5 Jahren, von denen 94 jährliche Visiten hatten, die zwischen 2009 und 2016 von einem Hornhautmikrochirurgen (B. S.) einer elektiven PKP mit normalem Risiko für nicht-infektiöse Indikationen unterzogen wurden.

Ergebnisse Unter den 216 Augen korrelierte die ECL (39,1 %) über 5 Jahre postoperativ schwach positiv mit der Lagerungslösungszeit ($p = 0{,}024$) und mit der postmortalen Zeit ($p = 0{,}028$) sowie mäßig positiv mit der präoperativen ECD ($p < 0{,}001$). Die postoperative 5-Jahres-ECL unterschied sich

signifikant zwischen in domo vorbereiteten (36,8 %) und ex domo Spenderhornhäuten (46,3 %; p = 0,001). Bei den 94 Augen wurden keine signifikanten Unterschiede zwischen den beiden Gruppen für die zentrale Pupillenpachymetrie (CCT) und den BCVA festgestellt (p > 0,074). Die CCT nahm jedoch zwischen 1 und 4 Jahren (p = 0,034) und 1 und 5 Jahren postoperativ (p = 0,012) signifikant zu. Der Visus verbesserte sich 1 Jahr postoperativ signifikant und verbesserte sich bis 2 Jahre postoperativ weiter (p < 0,001).

Schlussfolgerung Die Lions-Hornhautbank Saar-Lor-Lux erzielte eine signifikant geringere ECL (36,8 %) über 5 Jahre im Vergleich zu Ex-Domo-Spenderhornhäuten (46,3 %). Es wurde eine schwache positive Korrelation zwischen der ECL und der Dauer der Aufbewahrungslösung und der Post-mortem-Zeit sowie eine moderate positive Korrelation mit der präoperativen ECD festgestellt. Obwohl die CCT über 5 Jahre signifikant anstieg, verbesserte sich der Visus vom 1. zum 2. postoperativen Jahr signifikant und blieb danach stabil.

Introduction

The gradual loss of corneal endothelial cell density (ECD) after penetrating corneal transplantation is a crucial prognostic indicator for assessing the viability of the donor corneal tissue. It is well-known that corneal ECD progressively decreases over the long-term postoperative period and can eventually lead to failure of the transplanted corneal graft. Based on current recommendations of the European Eye Bank Association (EEBA), it is highly advisable to consider a donor ECD of ≥ 2000 cells/mm² before proceeding with corneal transplantation, as this value is widely accepted as a minimum requirement, although its basis is not firmly established in studies. The decrease of corneal ECD after corneal transplantation is much higher than after less invasive procedures, such as cataract surgery (2.5 % per year) [1] or in a healthy population (0.6 % per year) [2]. As an example, Bourne et al. reported the mean endothelial cell loss (ECL) to be 7.8 % per year for 5 years of follow-up after keratoplasty [3]. The mean ECL in comparison with the preoperative ECD was 58.9 % 5 years after keratoplasty.

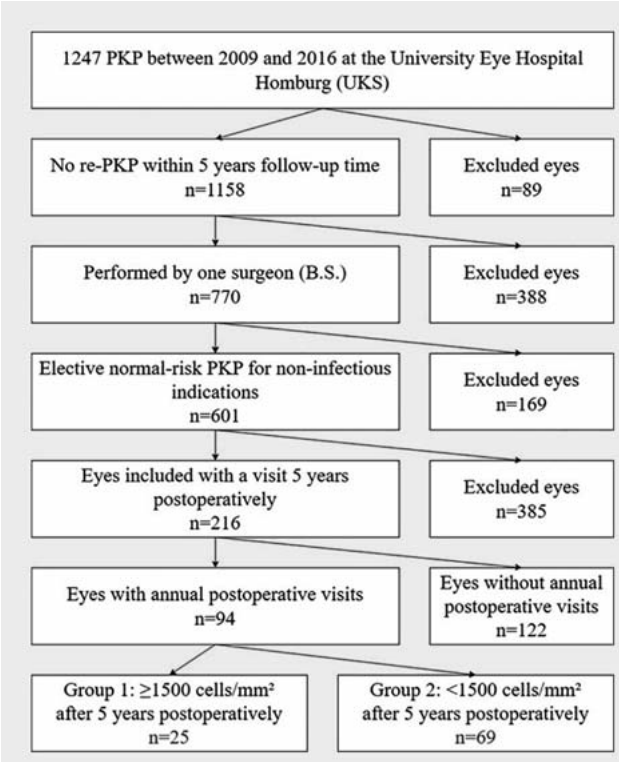
Penetrating keratoplasty (PKP), a transplantation procedure that replaces the full-thickness cornea, is a worldwide performed surgery to treat patients afflicted by corneal dystrophies, corneal scars, bullous keratopathy, and corneal shape abnormalities [4]. It is well known that corneal graft viability and transparency depend on how well the graft maintains a healthy ECD. Corneas with a central ECD below 1000 cells/mm² are considered at risk for swelling and decompensation, although corneas with a central ECD around 500 cells/mm² can still remain clear [5 – 7]. Thus, this study aimed to investigate the correlation between postoperative ECL and donor, host, and surgical parameters, and to assess the clinical impact of maintaining a "high" ECD of ≥ 1500 cells/mm² after 5 years post-PKP.

Patients and Methods

This single-center retrospective cohort study was approved by the Ethics Committee of the Saarland Medical Association, Germany (registration number 13/21). The data used for this study originated from the PKP database of Department of Ophthalmology, Saarland University Medical Centre, Homburg, Germany. Statistical analysis was performed using SPSS (Version 29, IBM SPSS Statistics, Armonk, New York, USA) and Excel 2021 (Microsoft 365, Microsoft Corp., Redmond, WA, USA). The data analysis incorporated a comprehensive set of suitable statistical tests, including t-test, paired t-test, Mann-Whitney U test, Wilcoxon test, chi-square test, general linear model (GLM), repeated measures ANOVA (MANOVA), and Pearson correlation test, adhering to the specific requirements of the study. Normality assumptions were assessed, and statistical significance was determined at a significance level of p < 0.05. The database contained, at the time of data extraction, 1247 primary cases, from January 2009 through July 2016. To reduce surgery-related bias, data from only one surgeon (B. S.) were used. To establish a more homogeneous patient population, we excluded all patients with infectious and noninfectious high-risk PKP. Of 770 consecutive eyes that underwent PKP by the same surgeon, 601 were left after exclusion by indication of the corneal transplantation.

Of those 601 eyes, 216 have revisited the university clinic 5 years postoperatively. The ECD of the included donor corneas was measured before transplantation and 5 years after PKP, of which 94 eyes were measured annually. The subpopulation (n = 94) who underwent annual postoperative visits at our hospital were categorized into two groups based on ECD at the 5-year postoperative mark: ≥ 1500 cells/mm² (group 1, n = 25, 26.5 %) and < 1500 cells/mm² (group 2, n = 69, 73.4 %; ▶ **Fig. 1**). In light of the existing data and the preoperative ECD in this study (mean 2425 cells/mm²), 1500 cells/mm² as an artificial cutoff were considered a "high" ECD 5 years postoperatively. We checked for correlation of the recipient (age, gender, diagnosis, and lens status), donor (age, preoperative ECD, postmortem time, storage solution time, graft origin), and surgical parameters (PKP or triple PKP, trephination size, trephination technique, suture type) with the ECL at the visit 5 years postoperatively (n = 216) to investigate potential influencing factors on long-term corneal ECD after PKP. Due to missing data, we could not take the gender of the donor into account. In order to analyze the clinical impact of the ECD difference further between the two groups of the subpopulation (n = 94), we compared the following factors: polymegethism and pleomorphism, visual acuity (best-corrected [BCVA] and uncorrected [UCVA]), and pachymetry at the apex and pupil center. The annual loss for the group with annual visits was calculated by a linear and exponential regression model [8].

As our standardized protocol for noninfectious normal risk elective PKP, all patients underwent an excimer laser-assisted PKP (a trephination size of 7.0 to 8.5 mm with a graft oversize of 0.1 mm) with a continuous double monofilament cross-stitch nylon 10-0 suture [9 – 13]. Of the donor corneal grafts, 73.6 % were surgically (sclerocorneal) removed and prepared for transplantation by the staff of the Klaus Faber Centre for Corneal Diseases includ-



▶ **Fig. 1** Flow chart illustrating the inclusion and exclusion criteria, as well as the grouping in this retrospective monocentric cohort study.

ing Lions corneal bank Saar-Lor-Lux, Trier/West Palatinate. The other donor corneas came from various other eye banks [14].

Postoperative ECD was measured with the same device and was recorded at 1, 2, 3, 4, and 5 years postoperative by using a noncontact specular microscope (Tomey specular microscope EM-4000, Nagoya, Japan automated measurement without manual correction). The preoperative ECD data were collected by our in domo eye bank through specular microscopy (Zeiss primovert digital microscope, Oberkochen, Germany automated measurement without manual correction) after manual identification of the central corneal endothelium in the donor's eye. Central pupil pachymetry (CCT) was measured using the Oculus Pentacam (Oculus Pentacam HR, Wetzlar, Germany).

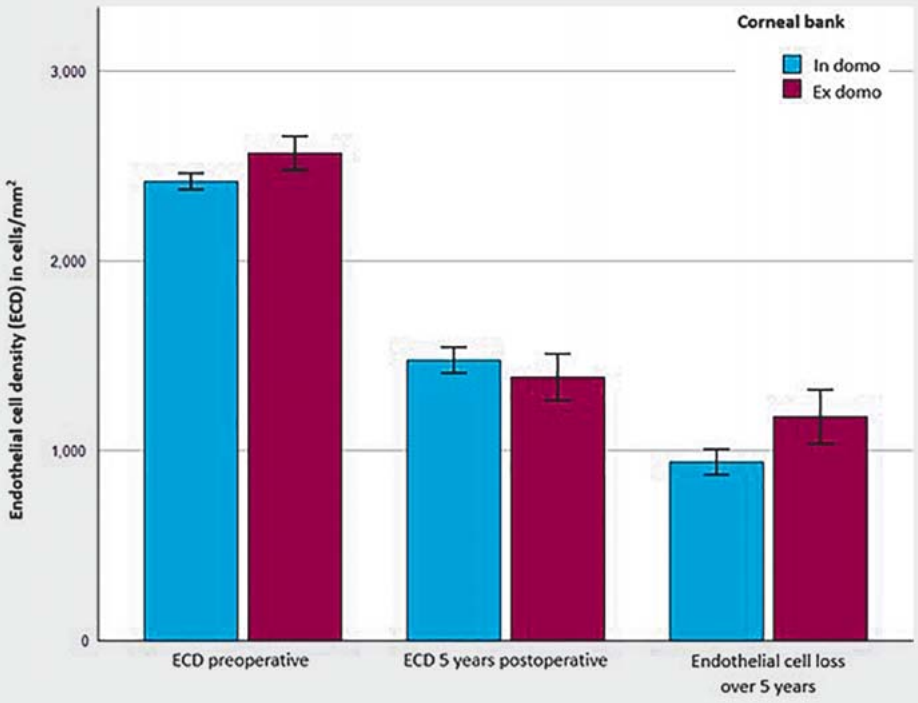
Results

For the 216 eyes included, a weak positive correlation was found between the ECL over a 5-year postoperative period and the storage solution time ($p = 0.024$, $r = 0.191$) and the postmortem time ($p = 0.028$, $r = 0.187$). Additionally, a moderate positive correlation was found between the ECL over a 5-year postoperative period and the preoperative ECD ($p < 0.001$, $r = 0.411$; ▶ **Table 1**). Furthermore, ECL over 5 years postoperatively differed significantly between donor corneas prepared by our Lions corneal bank Saar-Lor-Lux (36.8%) and those obtained from a corneal bank outside our institution (46.3%; $p = 0.001$; ▶ **Fig. 2**). For all 216 eyes, the preoperative ECD and the ECD after 5 years were 2425 ± 304 and 1477 ± 421 cells/mm² (mean ± SD), respectively. The mean ECL for all 216 eyes in comparison with the donor ECD was 39.1% over 5 years postoperatively.

The preoperative ECD of the 94 eyes with annual visits over 5 years postoperatively was 2410 ± 254 cells/mm². The ECL at

▶ **Table 1** The donor, recipient, and surgical parameters with their corresponding descriptives and p-values for the correlation with endothelial cell loss (ECL) over a follow-up period of 5 years postoperatively. All patients underwent excimer laser-assisted penetrating keratoplasty, accompanied by the uniform implementation of the suture type and technique.

Donor parameters (p-value for correlation with ECL)		**Descriptives**
Age in years ($p = 0.525$)	Mean ± standard deviation (SD)	63.9 ± 17.3
	Median	67
Preoperative endothelial cell density in cells/mm² ($p < 0.001$)	Mean ± SD	2435 ± 261
	Median	2400
Postmortem time in hours ($p = 0.028$)	Mean ± SD	15.8 ± 11.4
	Median	15.0
Storage solution time in days ($p = 0.024$)	Mean ± SD	9.9 ± 7.8
	Median	4.0
Graft origin ($p = 0.001$)	Corneal bank in domo	159 (73.6%)
	Corneal bank ex domo	57 (26.4%)
Recipient parameters (p-value for correlation with ECL)		
Age ($p = 0.631$)	Mean ± SD	51.9 ± 18.2
	Median	55
Gender ($p = 0.429$)	Male	135 (62.5%)
	Female	81 (37.5%)
Diagnosis ($p = 0.200$)	Corneal ectasia	120 (55.6%)
	Corneal dystrophy	42 (19.4%)
	Non-immunological graft rejection	28 (13.0%)
	Corneal scarring	26 (12.0%)
Lens status ($p = 0.430$)	Phakic	163 (75.5%)
	Pseudophakic with intraocular lens in the bag	46 (21.3%)
	Pseudophakic with intraocular lens in the ant. chamber	2 (0.9%)
	Aphakic	5 (2.9%)
Surgical parameters (p-value for correlation with ECL)		
Type of surgical procedure ($p = 0.296$)	Penetrating keratoplasty (PKP) only	201 (93.5%)
	Triple PKP	15 (6.5%)
Trephination size ($p = 0.167$)	≥ 8.0 mm	166 (81.4%)
	< 8.0 mm	38 (18.6%)



▶ **Fig. 2** A comprehensive evaluation (confidence interval of 95%) of endothelial cell density (ECD) and endothelial cell loss (ECL) in corneal grafts originating from the in domo and external corneal banks (ex domo). Over the 5-year observation period, the ECL for in-house grafts was found to be 36.8%, while the ECL for grafts from external sources was measured at 46.3% (p = 0.001).

5 years postoperatively was 1072 ± 485 cells/mm² (44.5 ± 20.1%). In the linear and exponential regression model, the ECD decreased annually by 222 ± 375 cells/mm² (9.2 ± 15.5%) and 17.8 ± 7.9%, respectively. The preoperative ECD of donor tissue of the 1st group (≥ 1500 cells/mm²) versus (vs.) the 2nd group (< 1500 cells/mm²) was 2428 ± 249 vs. 2404 ± 238 cells/mm². In the linear regression model, ECD decreased annually by 135 ± 325 cells/mm² (5.4 ± 13.0%) vs. 254 ± 364 cells/mm² (10.6 ± 15.3%), respectively. In the exponential regression model, ECD decreased annually by 16.5 ± 8.3 vs. 18.3 ± 7.1%. Total ECL at 5 years postoperatively was 675 ± 222 cells/mm² (27.1 ± 8.9%) vs. 1272 ± 354 cells/mm² (53.2 ± 14.8%; ▶ **Fig. 3**).

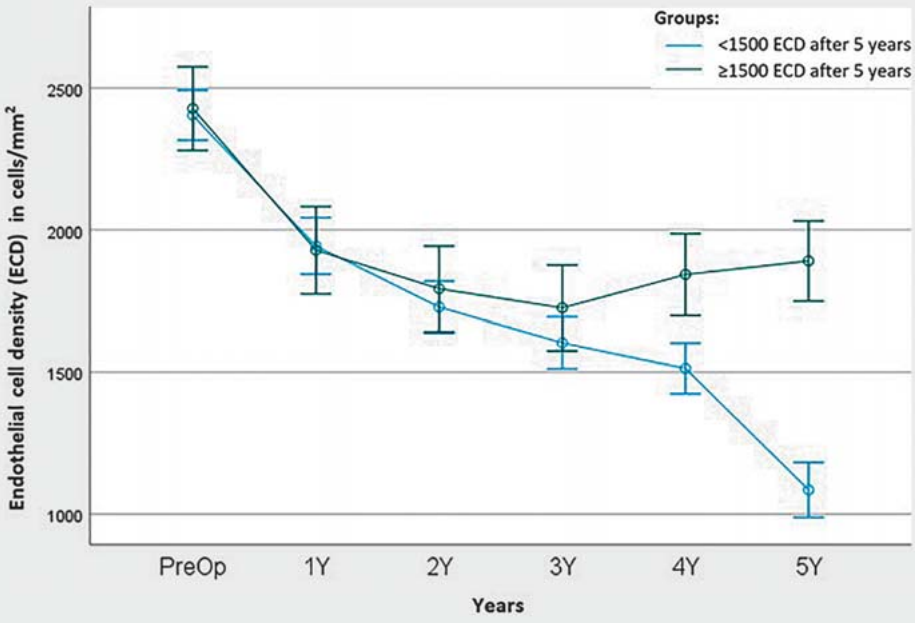
In the 94 eyes, CCT increased significantly between the 1st and 4th (p = 0.034) and the 1st and 5th year postoperatively (p = 0.012; ▶ **Fig. 4**). In addition, there was a significant increase in BCVA at 1 year postoperatively, which continued into the 2nd year postoperatively (p < 0.001; ▶ **Fig. 5**). The between-group p-values for CCT and BCVA were 0.190 and 0.074, respectively, after Bonferroni adjustment for multiple comparisons. No significant difference was found between the two groups in qualitative endothelial cell parameters (pleomorphism and polymegethism) (p ≥ 0.245).

Out of the 94 included eyes with annual visits, 4 eyes (4.3%) from 4 different patients had an "exceptionally high" ECD of ≥ 2000 cells/mm² 5 years postoperatively. The preoperative ECD was 2771 ± 231 cells/mm² in these cases. In the linear and exponential regression model, the ECD decreased annually by 111 ± 600 cells/mm² (4.0 ± 21.7%) and 15.9 ± 3.8% respectively. The total ECL after 5 years postoperatively was 556 ± 137 cells/mm² (24.5 ± 4.9%). They were aged between 19–27 years at the time of surgery, on average, 22.0 ± 3.6 years (mean ± SD). The median was 21 years, and all had a recipient diagnosis of keratoconus.

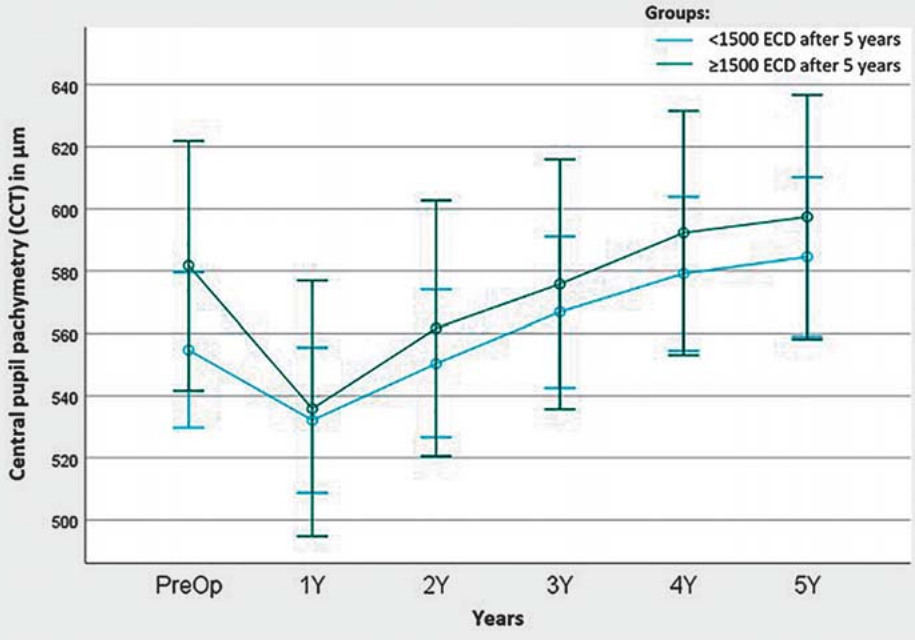
Discussion

The results of this retrospective study of patients who underwent a normal-risk elective PKP during the period from January 2009 to September 2016 revealed a weak positive correlation between the ECL over a 5-year postoperative period and the storage solution time (p = 0.024, r = 0.191) as well as the postmortem time (p = 0.028, r = 0.187). Additionally, our results showed a moderate positive correlation between the ECL over a 5-year postoperative period and the preoperative ECD (p < 0.001, r = 0.411; ▶ **Table 1**). This positive correlation means that the longer the storage solution and postmortem time, and the higher the preoperative ECD, the greater the ECL over a 5-year postoperative period. Furthermore, ECL over 5 years postoperatively differed significantly between donor corneas prepared by our Lions corneal bank Saar-Lor-Lux (36.8%) and those obtained from a corneal bank outside our institution (46.3%; p = 0.001; ▶ **Fig. 2**). The mean ECL for all 216 in comparison with the donor ECD was 39.1% over 5 years postoperatively.

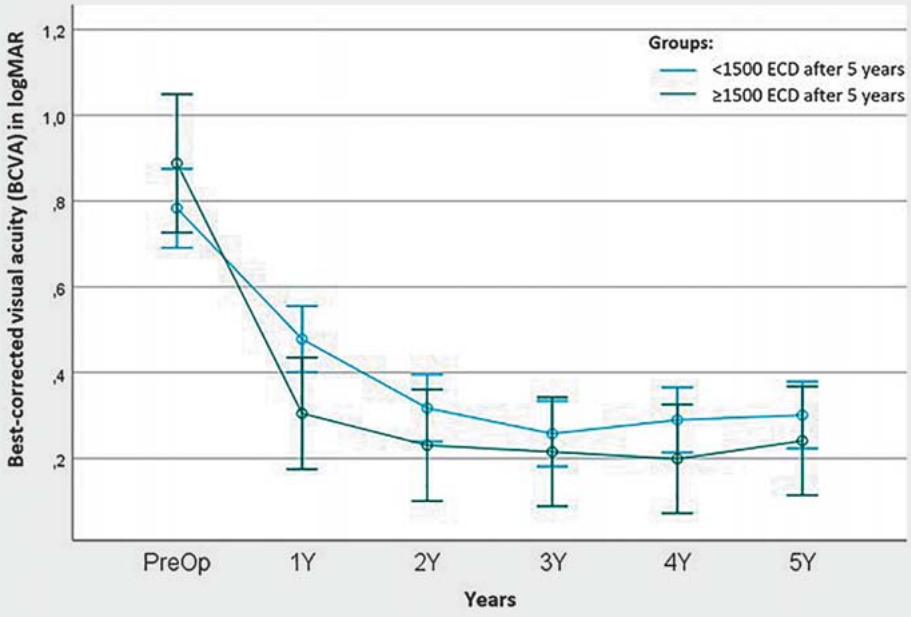
A subpopulation with annual visits (n = 94) was divided into two groups based on ECD at 5 years postoperatively: ≥ 1500



▶ **Fig. 3** The course of endothelial cell density (ECD) of both groups of the subpopulation of patients with annual postoperative visits (n = 94) from preoperative to 5 years postoperative with a confidence interval of 95%.



▶ **Fig. 4** The course of central pupil pachymetry (CCT) of both groups of the subpopulation of patients with annual postoperative visits (n = 94) from preoperative to 5 years postoperative with a confidence interval of 95%. After applying Bonferroni adjustments for multiple comparisons, the between-group p-value was found to be 0.190, suggesting that there was no statistically significant difference between the groups.



▶ **Fig. 5** The course of best-corrected visual acuity (BCVA) in logMAR of both groups of the subpopulation of patients with annual postoperative visits (n = 94) from preoperative to 5 years postoperative with a confidence interval of 95%. After applying Bonferroni adjustments for multiple comparisons, the between-group p-value was found to be 0.074, suggesting that there was no statistically significant difference between the groups.

cells/mm² (group 1) and < 1500 cells/mm² (group 2). Interestingly, both groups had approximately the same ECL during the first 3 postoperative years. Only in the 4th postoperative year, the ECL remained steady in the 1st group and increased rapidly in the 2nd group. Several studies suggested a biexponential decay model for ECL after PKP, which could fit the pattern of ECL of the 2nd group [15, 16]. Additionally, the vast majority of patients who underwent cataract surgery (n = 16, in 16 of 94 eyes [17.0%]) or developed a graft rejection (n = 20, in 16 of 94 eyes [17.0%]) during the postoperative course were in the 2nd group; this may serve – at least in part – as an explanation for this phenomenon. This suggests that the anterior chamber microenvironment plays an important role in maintaining a steady postoperative ECD. Only 4 patients of the subpopulation (4.3%) had an "exceptionally high" ECD of ≥ 2000 cells/mm² at 5 years postoperatively. They shared the recipient's diagnosis of keratoconus. Of particular interest was the average annual rate of ECL of approximately 4.0% (linear), which is considerably less than the ECL typically observed after a PKP.

In other studies, younger donor age, female gender, and larger graft diameter were all associated with a higher corneal ECD 5 years postoperatively, according to the Cornea Donor Study Investigator Group (CDS) findings [17 – 19]. According to previous studies, excimer laser-assisted keratoplasty has no disadvantages compared to mechanical trephination [20]. The recipient's age and the donor's ECD negatively and positively influence the postoperative ECD, respectively [21, 22]. Furthermore, a low recipient ECD is a risk factor for increased ECL after PKP [23]. In patients with inadequate ECD, a large trephine size could reduce chronic ECL. The ECL differs depending on the recipient's diagnosis due to the migration of endothelial cells along a density gradient after PKP [8]. ECL was found to be least pronounced after PKP in keratoconus, followed by Fuchs' endothelial dystrophy and pseudophakic bullous keratopathy [8, 16, 24]. This could explain the difference in ECL over 5 years post-PKP between our results (39.1%) and those of Bourne et al. [3] (58.9%), as they had a relatively lower number of corneal ectasia cases as an indication for surgery. Indeed, the recipient diagnosis of our 4 patients with an "exceptionally high" ECD (≥ 2000 cells/mm²) at 5 years postoperatively was keratoconus and is in line with the findings [8].

ECD is primarily a crucial prognostic indicator for assessing the survival rate of donor corneas, but the CCT and BCVA should also be considered before making clinical decisions. Cornea guttata on donor corneas affect the postoperative CCT and ECD, without affecting the postoperative BCVA at 1 year postoperatively [25]. In addition, corneal thickness could serve as a predictor of graft survival during the first 5 postoperative years. It was not a substitute for ECD measurement, because both measures were independently predictive for graft failure [26]. Our findings showed that despite a significant increase in CCT from 1 year to 4–5 years ($p < 0.034$) postoperatively, the BCVA remained stable over time starting from 2 years postoperatively ($p < 0.001$). Even in the absence of clinical signs of postoperative complications, patients with an increased corneal graft thickness above the normal limit for the postoperative time point are at an increased risk of graft failure [27, 28].

Limitations

In order to reduce surgical bias, it should be noted that we selected one surgeon (B.S.) who performed the most normal-risk elective PKPs in the given timespan without the use of the Homburg cross-stich marker according to Suffo et al. [9–11]. Second, to achieve a more accurate estimate of the annual postoperative ECL, a subpopulation of patients who completed an annual 5-year follow-up after PKP at our center was taken into calculation. Since the Department of Ophthalmology, Saarland University Hospital, is a tertiary reference center with patients traveling up to several hundred kilometers for corneal transplantation treatment, many patients (n = 385) prefer to have further regular checkups at local ophthalmologists after satisfactory postoperative outcomes. The same trend was observed in the context of younger patients with keratoconus, where generally positive clinical outcomes were noted, and a preference for discontinuing follow-up was frequently observed [29]. As a keratoconus reference center, keratoconus is one of our hospital's main indications for PKP [30]. Both inclusion criteria significantly reduced our study population finally available for assessment and are considered qualitatively improving, but also quantitatively limiting factors to our study. The aforementioned combined with a retrospective study setup leads to some degree of selection bias. The vast majority of the donor corneas originated from our cornea bank and cornea banks with which we have close relationships, resulting in a reduction of clinical bias due to differences between domestic and imported donor corneas [14, 31].

Conclusion

Our findings show a weak positive correlation between ECL over a 5-year postoperative period and storage solution time as well as the postmortem time. Additionally, our results showed a moderate positive correlation between the ECL over a 5-year postoperative period and the preoperative ECD. Furthermore, ECL over 5 years postoperatively differed significantly between donor corneas prepared by our Lions corneal bank Saar-Lor-Lux (36,8%) and those obtained from a corneal bank outside our institution (46.3%). The mean ECL in comparison with the donor ECD was 39.1% over 5 years postoperatively. Only from the 4th year postoperatively, the ECD decreased more rapidly in the second group (< 1500 cells/mm²). Despite a significant increase in CCT between 1 year and 4–5 years postoperatively, the BCVA remained stable over time.

Conflict of Interest

The authors declare that they have no conflict of interest.

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