



## 1. Introduction

Penetrating keratoplasty (PKP) is one of the most widely practiced and the most successful form of tissue transplantation in humans worldwide. Changes of corneal transplantation techniques and their instrumentation has accelerated during the last decades. Introduction of lamellar keratoplasty techniques decreased the proportion of PKPs all over the world.

The German Keratoplasty Registry found, that among the corneal transplantations, the proportion of PKPs decreased from 96.0% in 2006 to 40.1% in 2016. In contrast, percentage of posterior lamellar keratoplasties have increased from 14% in 2006 to 57% in 2016, and Descemet Membrane Endothelial Keratoplasty represented more than 90% of posterior lamellar keratoplasties.

In the USA, these trends were the same: percentage of PKPs decreased from 95.0% in 2005 to 46.0% in 2016 and percentage of posterior lamellar keratoplasties increased from 1.4% in 2005 to 58.4% in 2016.

*Matthaei* et al. recently reviewed 34 years of changing indications of penetrating keratoplasty, globally. They have shown, that the main indications vary by geographic regions. For example, in North America, the first or second main indications for PKP were pseudophakic or aphakic bullous keratopathy and regrant followed by keratoconus. In contrast, in the western part of Europe and Australia, the main PKP indication was keratoconus followed by pseudophakic or aphakic bullous keratopathy and keratitis. Instead, in Asia, the leading PKP indication was keratitis, followed by pseudophakic or aphakic bullous keratopathy and regrant.

Analysing changing trends in PKP indications may help to evaluate the need of corneal grafts and to plan corneal banking procedures along these. Therefore, from time to time it is indispensable to observe these trends in different geographical regions.

## **2. Objectives**

The objective of our research was to analyse the changing trends in penetrating keratoplasty indications in a Hungarian and German center between 2006 and 2018. In order to achieve this objective, the aims of the present study were:

**2.1.** To analyse the changing trends in penetrating keratoplasty (PKP) indications between 2006 and 2017, at the Department of Ophthalmology of Semmelweis University, Budapest, Hungary.

**2.2.** To analyse the changing trends in penetrating keratoplasty indications between January 2011 and December 2018, at the Department of Ophthalmology, Saarland University Medical Center, Homburg/Saar, Germany.

**2.3.** To analyse the effect of the introduction of posterior lamellar keratoplasty techniques on total number of keratoplasties and number of penetrating keratoplasties (PKP) due to corneal decompensation at the Department of Ophthalmology of Semmelweis University, Budapest, Hungary.

### **3. Methods**

#### **3.1. Changing trends in penetrating keratoplasty indications at the Department of Ophthalmology of Semmelweis University, Budapest, Hungary between 2006 and 2017**

This retrospective study included all patients who underwent PKP between 2006 and 2017 at the Department of Ophthalmology, Semmelweis University, Budapest. Patients' data were analysed with respect to age, sex and clinical diagnoses supported by the histological diagnoses of the explanted corneal buttons. Histological analysis was performed at the 1<sup>st</sup> and 2<sup>nd</sup> Departments of Pathology, Semmelweis University, Budapest, Hungary.

Between 2006 and 2012 there were two Departments of Ophthalmology at Semmelweis University (1st and 2nd Departments of Ophthalmology) which were merged in January 2013. Therefore, two different time-periods (2006-2012 and 2013-2017) were also analysed and compared concerning PKP indications.

The chi-square test was used to compare the number of corneal buttons in each group at both time-periods. A p value <0.05 was considered statistically significant.

#### **3.2. Changing trends in penetrating keratoplasty indications, at the Department of Ophthalmology, Saarland University Medical Center, Homburg/Saar, Germany between 2011 and 2018**

This retrospective study included all patients who underwent PKP between 2011 and 2018 at the Department of Ophthalmology, of Saarland University Medical Center, Homburg/Saar, Germany. Patients' data were analysed with respect to age, sex and clinical diagnoses supported by the histological diagnoses of the explanted corneal buttons. Histological analysis was performed at the

Department of Pathology of Saarland University Medical Center, Homburg/Saar, Germany.

In order to observe the changing trends in PKP indications, two different time-periods (2011-2014 and 2015-2018) were also analysed and compared (using chi-square test, p value <0.05), concerning PKP indications.

For classification of the corneal buttons at the Department of Ophthalmology of Semmelweis University and at the Department of Ophthalmology, Saarland University Medical Center, we used a nomenclature similar to previous reports. In case there was more than one histological diagnosis, the priority scheme suggested by *Brady* et al. was applied. Corneal buttons in our study were classified into nine groups as follows:

- pseudophakic or aphakic bullous keratopathy
- regraft
- corneal scar
- acute necrotizing and ulcerative keratitis
- keratoconus
- Fuchs' dystrophy
- corneal dystrophy other than Fuchs'
- failed posterior lamellar keratoplasty graft
- other diagnoses

### **3.3. Introduction of posterior lamellar keratoplasty techniques at the Department of Ophthalmology of Semmelweis University; effect on number of keratoplasties and penetrating keratoplasties due to corneal decompensation between 2008 and 2017**

In this retrospective study we analysed data of posterior lamellar keratoplasties and all other kinds of corneal transplantations between

2008 and 2017 at the Department of Ophthalmology, Semmelweis University, Budapest, Hungary. Beside the number of different types of corneal transplantations, the number of posterior lamellar keratoplasties and PKPs due to corneal decompensation have been compared. Based on the results of the histological examination following PKP, patients with corneal decompensations were classified with the diagnosis of pseudophakic or aphakic bullous keratopathy or Fuchs' dystrophy. In case of posterior lamellar keratoplasties due to corneal decompensation, histological analysis was not available.

## **4. Results**

### **4.1. Changing trends in penetrating keratoplasty indications at the Department of Ophthalmology of Semmelweis University, Budapest, Hungary between 2006 and 2017**

During the above-mentioned period, 1956 PKPs were performed and 1721 histological analyses of 1214 patients were available for review at the Department of Ophthalmology of Semmelweis University. Regarding the 1721 eyes, patient age at the time of surgery was  $62.5 \pm 18.3$  years, 805 (46.8%) were males and 851 right (49.4%) and 870 left eyes (50.6%) were operated.

In the past 12 years, PKP indications were pseudophakic or aphakic bullous keratopathy in 487 (28.3%), regrant in 443 (25.7%), acute necrotizing and ulcerative keratitis in 313 (18.2%), corneal scar in 153 (8.9%), keratoconus in 140 (8.1%), Fuchs' dystrophy in 61 (3.5%), corneal dystrophy other than Fuchs' in 46 (2.7%), other diagnoses in 44 (2.6%) and failed posterior lamellar keratoplasty graft in 34 (2.0%) cases.

The number of the PKPs between 2006 and 2012 (6 years,  $n=1118$ ) was a little bit less than double of those between 2013 and 2017 (5 years,  $n=603$ ). The commonest first three PKP indications were the same in both time-periods (pseudophakic or aphakic bullous

keratopathy, regrant, acute necrotizing and ulcerative keratitis). However, from the first to the second analysed time-period, incidence of acute necrotizing and ulcerative keratitis (from 16.7 to 20.9%;  $\chi^2=4.57$ ;  $p=0.032$ ), corneal scar (from 7.1 to 12.3 %;  $\chi^2=13.10$   $p<0.001$ ) and Fuchs' dystrophy (from 2.7 to 5.1 %;  $\chi^2=6.92$ ;  $p=0.008$ ) increased and incidence of keratoconus significantly decreased (from 9.3 to 6.0%;  $\chi^2= 5.82$ ;  $p=0.015$ ) among PKP patients. The proportion of the pseudophakic or aphakic bullous keratopathy patients decreased slightly from 30.1% to 25.0% ( $\chi^2=3.23$ ;  $p=0.07$ ), those of regravts from 27.2% to 23.1% ( $\chi^2=3.51$ ;  $p=0.06$ ) from first to second time-period, without statistically significant difference.

#### **4.2 Changing trends in penetrating keratoplasty indications, at the Department of Ophthalmology, Saarland University Medical Center, Homburg/Saar, Germany between 2011 and 2018**

During the analysed time-period, 2232 PKPs were performed and 2123 histological analyses were available for evaluation. The 2123 PKPs were performed on 1993 eyes (1017 left eyes) and 56% were males, age of the patient at the time of surgery was  $57.6\pm 18.7$  years.

During the analysed 8 years, the histopathological diagnoses were keratoconus in 455 (21.5%), acute necrotizing and ulcerative keratitis in 384 (18.1%), regrant in 367 (17.3%), corneal scar in 350 (16.5%), pseudophakic or aphakic bullous keratopathy in 225 (10.6%), Fuchs' dystrophy in 194 (9.1%), other diagnoses in 64 (3.0%), corneal dystrophy other than Fuchs' in 52 (2.4%), and failed posterior lamellar keratoplasty graft in 32 (1.5%) cases.

Analysing the two different time-periods (2011-2014 and 2015-2018), the number of PKPs between 2011 and 2014 (4 years,  $n=896$ ) was 1.37x less than between 2015 and 2018 (4 years,  $n=1227$ ). Keratoconus was the main PKP indication between 2011 and 2014 and the second most common indication between 2015 and 2018.

From the first to the second analysed time-period, percentage of PKPs for keratoconus changed from 23.9 to 19.6%, without statistical significant difference ( $\chi^2=3.56$ ;  $p=0.06$ ). The acute necrotizing and ulcerative keratitis became the main indication in the second time-period and its incidence increased significantly (from 14.1 to 21.1%  $\chi^2= 12.55$ ;  $p<0.001$ ). The percentage of PKPs for corneal scar (from 17.0 to 16.1 %;  $\chi^2=0.18$   $p=0.67$ ), pseudophakic or aphakic bullous keratopathy (from 10.5 to 10.7 %;  $\chi^2=0.01$ ;  $p=0.90$ ), corneal dystrophy other than Fuchs' (from 2.2 to 2.6%  $\chi^2=0.29$ ;  $p=0.59$ ) and other diagnosis (from 2.6 to 3.3%;  $\chi^2=1.00$ ;  $p=0.59$ ) did not change significantly. The incidence of regrant (from 14.8 to 19.1%;  $\chi^2= 4.56$ ;  $p=0.03$ ) increased significantly, and failed posterior lamellar keratoplasty graft did not change (from 0.7 to 2.1%;  $\chi^2=7.12$   $p=0.07$ ) comparing the two time-periods. In contrast, the percentage of PKPs for Fuchs' dystrophy (from 14.4 to 5.3 %;  $\chi^2=100.20$ ;  $p<0.001$ ) decreased significantly.

#### **4.3 Introduction of posterior lamellar keratoplasty techniques at the Department of Ophthalmology of Semmelweis University; effect on number of keratoplasties and penetrating keratoplasties due to corneal decompensation between 2008 and 2017**

During the analysed 10 years, 1715 eyes of 1237 patients underwent corneal transplantation. Age of the patients at the time of the surgery was  $61.4 \pm 16.5$  years.

Anterior lamellar keratoplasty have been performed in 53 eyes of 48 patients (29 (60.4%) male) (3.1% of all keratoplasties). Patient age at the time of surgery was  $55.5 \pm 20.6$  years for this group.

Penetrating keratoplasty have been performed in 1474 eyes of 1040 patients (85.9% of all keratoplasties). In this group, the mean age at the time of surgery was  $63.6 \pm 17.9$  years, with 699 (47.4%) male patients.

PKP have been performed due to pseudophakic or aphakic bullous keratopathy in 361 (21.5%) cases (age  $71.6 \pm 17.1$  years, 164 (44.6%) male) and due to Fuch's dystrophy in 54 (3.2%) cases (mean age  $68.5 \pm 16.2$  years, 19 (33.9%) male). Both indications have been verified by histological diagnosis.

Primary posterior lamellar keratoplasty have been performed in 169 eyes of 152 patients (9.6% of all keratoplasties), patient age at the time of the surgery was  $72.1 \pm 17.8$  years.

The total number of corneal transplantations and the number of PKPs decreased with 30-40% during the analysed time-period. Following introduction of posterior lamellar keratoplasty techniques, the number of PKPs due to pseudophakic or aphakic bullous keratopathy and Fuch's dystrophy was approximately 40% less every year.

## **5. Conclusions**

The current thesis sought to analyse the substantial data and important results of the changing trends in penetrating keratoplasty indications in a Hungarian and German center between 2006 and 2018. Based upon these results, the following conclusions are made:

**5.1.** Pseudophakic or aphakic bullous keratopathy is the leading indication for PKP at the Department of Ophthalmology of Semmelweis University, followed by regraft and acute necrotizing and ulcerative keratitis. Introduction of posterior lamellar keratoplasty techniques in 2009 did not change this order. Advancement in corneal banking and a better referral system of patients to corneal subspeciality centers should change this order in the next decades in Hungary.

**5.2.** With introduction of posterior lamellar keratoplasty, keratoconus remains the leading PKP indication at the Department of Ophthalmology, Saarland University Medical Center with excimerlaser-trephination on a routine basis. A trend towards increasing numbers can be observed regarding acute necrotizing and ulcerative keratitis patients and regrafts. However, the incidence of Fuchs' dystrophy decreased dramatically within PKP patients, with the introduction of posterior lamellar keratoplasty.

**5.3** With introduction of posterior lamellar keratoplasty techniques, the annual number of PKPs due to bullous keratopathy decreased at the Department of Ophthalmology of Semmelweis University, similar to other countries. However, the total number of corneal transplantations also decreased. Introduction of posterior lamellar keratoplasties may also result in increasing number of corneal transplantations in Hungary, in case of development in corneal banking.

## **6. Bibliography of the candidate's publications**

### **Thesis related publications**

1. Pluzsik MT, Seitz B, Flockerzi FA, Langenbacher A, Tóth G, Bohle RM, Szentmáry N. (2020) Changing trends in penetrating keratoplasty indications between 2011 and 2018 - Histopathology of 2123 corneal buttons in a single center in Germany. *Curr Eye Res*, Mar 13:1-6. Online ahead of print.  
**IF: 1.754**
2. Pluzsik MT, Tóth G, Tóth J, Matolcsy A, Langenbacher A, Kerényi A, Nagy ZZ, Szentmáry N. (2020) Changing trends in penetrating keratoplasty indications at a tertiary eye care center in Budapest, Hungary between 2006 and 2017. PKP indications at a tertiary eye care center. *Int J Ophthalmol*, 13: 1814-1819.  
**IF: 1.330**
3. Pluzsik MT, Tóth G, Németh O, Kerényi Á, Nagy ZZ, Szentmáry N. (2020) [Introduction of posterior lamellar keratoplasty techniques at the Department of Ophthalmology of Semmelweis University; effect on number of keratoplasties and penetrating keratoplasties due to corneal decompensation between 2008 and 2017]. *Szemészet*, 1: 36-41.

### **Other publications**

1. Pluzsik MT, Schneider M. (2014 ) [Bilateral idiopathic choroidal folds]. *Orvosi Hetilap*, 155: 1083-1086.
2. Tóth G, Szentmáry N, Sándor GL, Csákány B, Maka E, Tóth J, Antus Z, Pluzsik MT, Langenbacher A, Nagy ZZ, Lukáts O.

- (2019) Clinicopathological review of 547 bulbar enucleations in Hungary (2006-2017). *J Ophthalmol*, 6:1-7 **IF: 1.447**
3. Tóth G, Pluzsik MT, Sándor GL, Németh O, Lukáts O, Nagy ZZ, Szentmáry N. (2020) Clinical review of microbial corneal ulcers resulting in enucleation and evisceration in a tertiary eye care center in Hungary. *J Ophthalmol*, 3:1-8 **IF: 1.447**
  4. András B, Pluzsik MT, Pregun T, Bársony V, Pek G, Hargitai J, Enyedi L, Kálmán R, Hegedüs J, Toth E, Dékány S, Kerényi A. (2020) [Changing indications and surgical techniques for corneal transplantation at Bajcsy-Zsilinszky Hospital, Department of Ophthalmology - a 13 year review]. *Szemészet*, 1: 28-35.
  5. Tóth G, Pluzsik MT, Sándor GL, Csákány B, Antus Z, Lukáts O, Nagy ZZ, Szentmáry N. (2020) Indications for ocular evisceration and orbital implant related complications in a tertiary eye hospital in Hungary over a 11-year period. *Develop Heal Sci*, in press.
  6. Kovács Klaudia, Szentmáry N, Pluzsik MT, Langenbacher A, Kiss H, Füst Á, Kriskó D, Rác G, Matolcsy A, Nagy ZZ. (2020) [Graft survival using cadaver and multiorgan donors between 2008 and 2017 at our clinic]. *Orvosi Hetilap*, in press. **IF: 0.497**