• Investigation •

Changing trends in penetrating keratoplasty indications at a tertiary eye care center in Budapest, Hungary between 2006 and 2017

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Abstract

● **AIM:** To analyze the changing trends in penetrating keratoplasty (PKP) indications.

● **METHODS:** This retrospective study included all patients with PKP between 2006 and 2017. Patients were classified using histological diagnoses. Our groups were as the following: pseudophakic or aphakic bullous keratopathy, regraft, acute necrotizing and ulcerative keratitis, keratoconus, Fuchs' dystrophy, corneal dystrophy other than Fuchs', corneal scar, other diagnoses and failed endothelial keratoplasty graft. Additionally, two different time-periods (2006-2012 and 2013-2017) were analysed.

● **RESULTS:** Totally 1721 histological analyses of 1214 patients were available for review. The diagnoses were pseudophakic or aphakic bullous keratopathy in 487 (28.3%), regraft 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 endothelial keratoplasty graft in 34 (2.0%) cases. From the first to the second analysed time-period, incidence of acute necrotizing and ulcerative keratitis, corneal scar, Fuchs' dystrophy increased ($P \leq 0.032$ for all) and incidence of keratoconus significantly decreased ($P=0.015$).

● **CONCLUSION:** Pseudophakic or aphakic bullous keratopathy is the leading indication for PKP, followed by regraft and acute necrotizing and ulcerative keratitis.

● **KEYWORDS:** penetrating keratoplasty; indications; histology

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INTRODUCTION

Eduard Zirm performed the first successful human full-thickness corneal transplantation [penetrating keratoplasty (PKP)], in 1905[1]. The last 50y, PKP became the most successful type of tissue transplantation in humans[2].

Clinical indications for PKPs and histopathological diagnosis of the corneal buttons vary by geographical regions. Pseudophakic or aphakic bullous keratopathy was the most common indication for PKP and regraft the second major indication in North America from 1980 to 2012[3-5]. In Europe, Germany, the first most common PKP indication was keratoconus and the second Fuchs' dystrophy between 2001 and 2010[6]. In Hungary, pseudophakic bullous keratopathy or aphakic bullous keratopathy was the primary and regraft the secondary most common indication from 1993 to 2003[7]. In the developing countries, between the end of the 1990s to the beginning of 2000, keratitis was the leading indication for PKP[8-9].

Advancement in corneal transplantation techniques was gathering pace the last decade, allowing selective replacement of corneal layers. The patient's healthy endothelium is preserved during anterior lamellar keratoplasty, therefore, there

Table 1 Penetrating keratoplasty indications annually between 2006 and 2017 *n* (%)

Indication	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total
Corneal scar	16 (8.1)	12 (7.1)	9 (5.2)	15 (7.7)	11 (6.7)	10 (8.1)	6 (6.3)	20 (18.9)	13 (11.1)	14 (9.8)	16 (13.0)	11 (9.6)	153 (8.9)
Regraft	37 (18.7)	41 (24.1)	51 (29.7)	60 (30.8)[a]	43 (26.1)	44 (35.8)[a]	28 (29.5)[a]	24 (22.6)	25 (21.4)	29 (20.3)	27 (22.0)	34 (29.8)[a]	443 (25.7)
Pseudophakic or aphakic bullous keratopathy	64 (32.3)[a]	62 (36.5)[a]	54 (31.4)[a]	58 (29.7)	44 (26.7)[a]	37 (30.1)	17 (17.9)[a]	20 (18.9)	34 (29.1)[a]	31 (21.7)	35 (28.5)[a]	31 (27.2)	487 (28.3)[a]
Ulcerative keratitis	43 (21.7)	26 (15.3)	26 (15.1)	27 (13.8)	35 (21.2)	13 (10.6)	17 (17.9)	25 (23.6)[a]	20 (17.1)	38 (26.6)[a]	17 (13.8)	26 (22.8)	313 (18.2)
Fuchs' dystrophy	6 (3.0)	1 (0.6)	7 (4.1)	4 (2.1)	6 (3.6)	0	6 (6.3)	3 (2.8)	3 (2.6)	10 (7.0)	9 (7.3)	6 (5.3)	61 (3.5)
Keratoconus	21 (10.6)	18 (10.6)	12 (7.0)	11 (5.6)	18 (10.9)	12 (9.8)	12 (12.6)	9 (8.5)	8 (6.8)	10 (7.0)	8 (6.5)	1 (0.9)	140 (8.1)
Corneal dystrophy other than Fuchs'	3 (1.5)	5 (2.9)	5 (2.9)	6 (3.1)	3 (1.8)	2 (1.6)	1 (1.1)	0	8 (6.8)	9 (6.3)	2 (1.6)	2 (1.8)	46 (2.7)
Others	8 (4.0)	5 (2.9)	7 (4.1)	7 (3.6)	1 (0.6)	0	5 (5.3)	3 (2.8)	3 (2.6)	1 (0.7)	3 (2.4)	1 (0.9)	44 (2.6)
Failed endothelial keratoplasty graft	0	0	1 (0.6)	7 (3.6)	4 (2.4)	5 (4.1)	3 (3.2)	2 (1.9)	3 (2.6)	1 (0.7)	6 (4.9)	2 (1.8)	34 (2.0)
Total	198 (100)	170 (100)	172 (100)	195 (100)	165 (100)	123 (100)	95 (100)	106 (100)	117 (100)	143 (100)	123 (100)	114 (100)	1721 (100)

[a]The most common penetrating keratoplasty diagnoses.

is significantly lower postoperative endothelial cell loss and risk for graft rejection, during this procedure[10-12]. Concerning posterior lamellar keratoplasty, minimal invasiveness, significantly lower rejection reaction risk, a slight refractive shift and rapid visual amelioration are the main advantages, compared to PKP[11,13-14]. Therefore, the number of penetrating grafts is decreasing worldwide[15-16].

Our purpose was to examine the changing trends in PKP indications from 2006 to 2017, at the Department of Ophthalmology of Semmelweis University, Budapest, Hungary.

SUBJECTS AND METHODS

Ethical Approval This study was approved by the Institutional Board of Semmelweis University. The principles outlined in the Declaration of Helsinki have been followed. Written informed consent was obtained from the patients.

Our retrospective study analysed all patients with PKP from January 2006 to December 2017 at the Department of Ophthalmology, Semmelweis University, Budapest, Hungary. Patients' data were analysed with respect to age, sex and clinical diagnoses supported by the histological diagnoses of the explanted corneal buttons. The 1st and 2nd Departments of Pathology of Semmelweis University performed the histological examination.

Patients were classified using histological diagnoses similar to other reports, based on the priority scheme[6-7,17]. This means that in case of more than one histological diagnosis, Brady *et al*'s[3] priority scheme was used. As an example, the diagnosis was regraft, although there was another histological diagnosis[3]. Additionally, for Fuchs' dystrophy and bullous keratopathy, the described diagnosis was Fuchs' dystrophy[6-7]. We also defined the supplementary group "failed endothelial keratoplasty graft". This additional category has been specified in order to be able to focus on the posterior lamellar keratoplasty techniques, as its incidence was increasing in the last decade.

Therefore, in the present work, the nine following groups have been used for the classification of the corneal grafts: pseudophakic or aphakic bullous keratopathy, regraft, acute necrotizing and ulcerative keratitis, corneal scar, keratoconus, Fuchs' dystrophy, corneal dystrophy other than Fuchs', other diagnoses and failed endothelial keratoplasty graft.

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 time-periods (2006-2012 and 2013-2017) underwent analysis and have been compared regarding PKP indications. We used the Chi-square test for comparison of the corneal button numbers in every single group at both analysed time-periods.

RESULTS

From January 2006 to December 2017, there were 1956 PKPs. Histological report was accessible for 1721 corneal buttons of 1214 patients at the Department of Ophthalmology of Semmelweis University. Regarding the 1721 eyes, the age of patients was 62.5±18.3y (range 0-94y) at the time of surgery, 805 (46.8%) were males and 851 right (49.4%) and 870 left eyes (50.6%) were operated.

In the past 12y, PKP indications were pseudophakic or aphakic bullous keratopathy in 487 (28.3%), regraft 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 endothelial keratoplasty graft in 34 (2.0%) cases (Table 1, Figure 1).

The quantity of the PKPs from 2006 to 2012 (6y, *n*=1118) was a little bit less than double of those between 2013 and 2017 (5y, *n*=603). The commonest first three PKP indications were the same in both time periods (pseudophakic or aphakic bullous keratopathy, regraft, 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%; χ^2=4.57; P=0.032), corneal scar (from 7.1% to 12.3%; χ^2=13.10, P<0.001) and Fuchs' dystrophy (from 2.7% to 5.1%; χ^2=6.92; P=0.008) increased and incidence of keratoconus significantly decreased (from 9.3% to 6.0%; χ^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% (χ^2=3.23; P=0.07), those of regraft from 27.2% to 23.1% (χ^2=3.51; P=0.06) from first to second time-period, without statistically significant difference. PKP indications during two time periods are shown at Figure 2.

For repeat grafts, the histological diagnosis was endothelial dysfunction in 321 (72.5%), graft rejection in 90 (20.3%), ulcerative keratitis in 22 (5.0%) and donor necrosis and neovascularization in 10 cases (2.3%; Table 2).

In "acute necrotizing and ulcerative keratitis" patients, microorganisms have been described through histological diagnosis in 85 cases (27.1%). In 40 eyes (12.8%) viral, in 26 cases (8.3%) fungal, in 14 cases (4.4%) bacterial and in 5 cases (1.6%) *Acanthamoeba* keratitis could be histologically described. The distribution of corneal dystrophies other than Fuchs' is shown in Figure 3.

Regarding the analysed groups, patient age at the time of surgery was 69.9±13.3y in pseudophakic or aphakic bullous keratopathy (59.5% females), 65.9±16.8y in regraft (51.6% females), 60.4±18.0y in acute necrotizing and ulcerative keratitis (45.7% females), 56.7±19.2y in corneal scar (45.7% females), 68.4±9.2y in Fuchs' dystrophy (70.4% female), 52.4±20.3y in corneal dystrophy other than Fuchs' (54.3% females), 52.9±17.3y in other diagnoses (61.3% females) and 70.1±11.5y in failed endothelial keratoplasty graft (76.4% females) groups. Keratoconus patient age at the time of surgery was 37.7±15.2y and 34.2% were females.

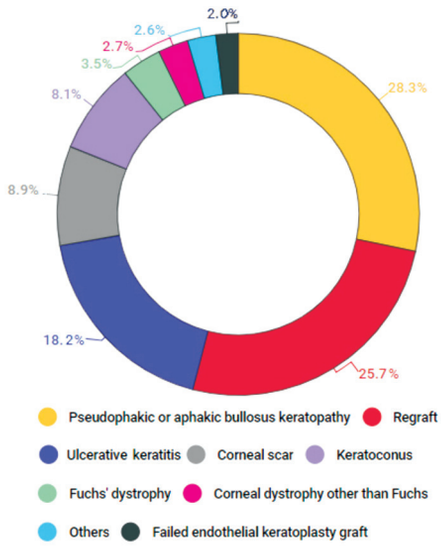

Figure 1 PKP indications from 2006 to 2017 (%), at the Department of Ophthalmology of Semmelweis University.

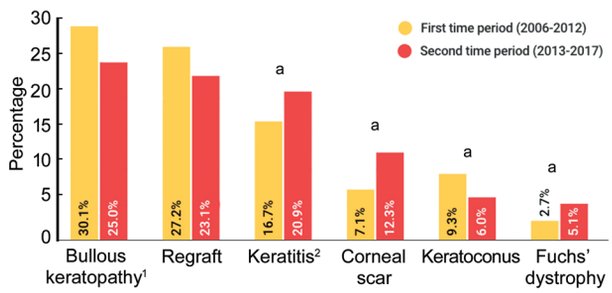

Figure 2 PKP indication in the first (2006-2012) and second (2013-2012) time periods at the Department of Ophthalmology of Semmelweis University [1]Bullous keratopathy: Pseudophakic or aphakic bullous keratopathy; [2]Keratitis: Acute necrotizing and ulcerative keratitis. [a]P<0.05.

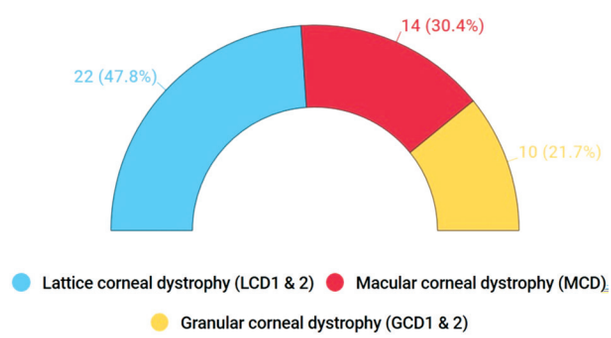

Figure 3 Histological diagnoses of corneal dystrophies other than Fuchs' from 2006 to 2017, *n* (%), at the Department of Ophthalmology of Semmelweis University.

DISCUSSION

There are 1721 keratoplasties from the Department of Ophthalmology of Semmelweis University, Budapest over 12y, from January 2006 to December 2017, summarized in our present study, based on histopathological analysis. In the previous study from our clinic between 1992-2003 the major indication for PKP was pseudophakic or aphakic bullous keratopathy (43.4%), followed by regraft (14.2%), ulcer and keratitis (14.2%), keratoconus (9.4%), corneal scar (8.8%), Fuchs' dystrophy (5.7%), corneal dystrophy other than Fuchs' (2.0%) and others (1.9%)[7]. Comparing the previous study (11y) with our current data from the last 12y, the order of the main PKP indications did not change, except the diagnoses of keratoconus and corneal scars which have reversed their order. A global review[18] of 34y of changing indications of PKP have described, that the principal indications were different by geographic regions. The first or second common PKP indications in North America were pseudophakic or aphakic bullous keratopathy and regraft and only the next main indication was keratoconus. In contrast, in the western part of Europe and Australia, keratoconus was the principal PKP indication, thereafter, the next leading indications were pseudophakic or aphakic bullous keratopathy and keratitis.

Table 2 Histological diagnosis of repeat penetrating keratoplasties from 2006 to 2017 *n* (%)

Indication	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total
Endothelial dysfunction	31 (83.8)[a]	22 (53.7)[a]	36 (70.6)[a]	43 (71.7)[a]	32 (74.4)[a]	31 (70.5)[a]	20 (71.4)[a]	19 (79.2)[a]	23 (92.0)[a]	23 (79.3)[a]	18 (66.7)[a]	23 (67.6)[a]	321 (72.5)[a]
Ulcerative keratitis	4 (10.8)	12 (29.3)	15 (29.4)	14 (23.3)	8 (18.6)	12 (27.3)	5 (17.9)	5 (20.8)	1 (4.0)	3 (10.3)	6 (22.2)	5 (14.7)	22 (5.0)
Donor necrosis and neovascularization	1 (2.7)	4 (9.8)	0	2 (3.3)	2 (4.7)	0	2 (7.1)	0	1 (4.0)	2 (6.9)	2 (7.4)	6 (17.6)	10 (2.3)
Graft rejection	1 (2.7)	3 (7.3)	0	1 (1.7)	1 (2.3)	1 (2.3)	1 (3.6)	0	0	1 (3.4)	1 (3.7)	0	90 (20.3)
Total	37 (100)	41 (100)	51 (100)	60 (100)	43 (100)	44 (100)	28 (100)	24 (100)	25 (100)	29 (100)	27 (100)	34 (100)	443 (100)

[a]The most common indications.

Instead, in Asia, keratitis was the main PKP indication, pursued by pseudophakic or aphakic bullous keratopathy and regraft.

In our Department, during 12y, pseudophakic or aphakic bullous keratopathy (28.3%; confirmed by histological diagnosis) was the common PKP indication, which is in accordance with studies from North America in the United States between 1982 and 1996[4] and Canada from 1995 to 2005[5]. In North America, the number of PKPs due to pseudophakic or aphakic bullous keratopathy have shown a decreasing trend, recently[7].

Bullous keratopathy is no longer the principal PKP indication in the developed countries. First, with the improvement of viscoelastic materials[19] and intraocular lens technology and cataract surgery technics[20], its incidence decreases. Second, with the development of endothelial keratoplasty techniques [Descemet stripping automated endothelial keratoplasty (DSAEK) and Descemet membrane endothelial keratoplasty (DMEK)] fewer patients undergo PKP for endothelial decompensation[21-22]. Due to this reason, in Germany, the percentage of posterior lamellar keratoplasties increased from 1.4% to 57% between 2006 and 2016 and the percentage of PKPs decreased from 96% to 40.1% during the same period[23]. At the Department of Ophthalmology of Semmelweis University, there was an introduction of posterior lamellar keratoplasties in 2008 with DSAEK and in 2017 with DMEK. The percentage of posterior lamellar keratoplasty grafts have been increasing to 10%-20% of all corneal transplantations over the last few years (data not shown) and with this relative low percentage, a significant decrease of PKP patients with bullous keratopathy could not be observed over the years in our series. In our observed patient population, the percentage of PKPs for pseudophakic or aphakic bullous keratopathy have shown a slightly decreasing trend in from 2006 to 2017. Most interestingly, we could not see the same trend for Fuchs' dystrophy, its incidence increased significantly between PKP patients from the first to the second time-period. This could be explained through the fact that Fuchs' dystrophy patients are referred relative late (with significant stromal scarring) to corneal surgery centres in Hungary.

In Budapest, the second main PKP indication was regraft (25.7%), alike Scotland (19.2%)[24], the USA (22.0%)[25] and India (11.5%)[8]. Concerning other European countries, for example Germany, it was only the sixth most common indication (7.0%)[6], and in Greece the third (11.9%)[26].

In a report from the UK[27], endothelial dysfunction (41.8%) and graft rejection (16.5%) were also lower than in our study. Analyzing percentage of regrafts though endothelial dysfunction (72.5% in our series), the source and quality of donor material have to be addressed. About 80% of our donor tissues were delivered through a cornea bank, using cold storage [Optisol GS, endothelial cell density (ECD) above 2000 cell/mm^2 at one single measurement]. Another 20% originated from multiorgan donors (also cold storage), nevertheless, ECD was not determined before the use of donor tissue. In our opinion, lack of repeat ECD measurements in both cases could have been one reason for the relatively high percentage of regrafts due to endothelial dysfunction in our series. Nevertheless, lack of patient cooperation may also have increased these numbers.

The third principal PKP indication was acute necrotizing and ulcerative keratitis (18.2%) in the present study. This is similar to other European countries like Greece (13.1%)[26], but differs from the USA (7.2%)[25]. There are many studies from Asia, where keratitis is the main PKP indication[8,28-29].

In our study in 13% cases viral, 8.3% fungal, 4.4% bacterial and 1.6% cases *Acanthamoeba* keratitis have been be verified histologically. The percentage of the all keratitis types was lower than in a study from Poland between 2010 and 2017 with 26% bacterial, 14% fungal and 4.25% *Acanthamoeba* keratitis diagnosis[30]. However, they did not report on incidence of herpetic keratitis. The percentage of the successful histologically diagnosed infectious keratitis types was lower in Hungary than in Poland. In contrast, in Vietnam, the commonest infectious keratitis type was fungal from 2002 to 2012, with an incidence of 53.1%. There were 33.3% bacterial, 8.4% viral and 2.2% *Acanthamoeba* keratitis there[31], which is explained mainly with the climatic differences between these lands.

The fourth principal PKP indication was corneal scarring (8.9%) in the current study. In India and China, one main PKP indication is keratitis. In addition, the main cause of

corneal scarring is healed infectious keratitis and traumatic corneal scars[8,29]. According to our study, the proportion of keratoplasties for corneal scarring (8.9%) has been reported to be lower than in those countries (28.1%-38.0%), similar to the lower incidence of infectious keratitis in our country[8,32-33].

The fifth main PKP indication in Budapest was keratoconus (8.1%), 65.7% of the patients were males. Incidence of keratoconus among PKP patients agrees with studies from Canada (12.0%)[34] and developing countries, such as China (13.0%)[29] and India (2.37%)[8,35], where a PKP for keratoconus is seldom. Nevertheless, in other European countries such as Germany[6] and Great Britain[24], keratoconus is the leading PKP indication. In our opinion, as prevalence of keratoconus is also reported to be lower in some developed countries, such as the United States (54.5 cases per 100 000 people)[36] and *e.g.* Netherlands (265 cases per 100 000 people)[37], the low percentage of PKPs in keratoconus may be related to the lower incidence of keratoconus disease in Hungary. Nevertheless, population-based studies still have not been performed in Middle-Europe.

In our study the proportion of PKPs for keratoconus decreased from 2006 to 2017. This may be related to the fact that some adjacent eye centres started with PKPs and increased their yearly PKP quote over the years in Budapest, at the same period. This is also displayed in the decreasing trend of the total number of PKPs at Semmelweis University.

The sixth main PKP indication was Fuchs' endothelial dystrophy (3.5%) in our study. Interestingly, the rate of Fuchs' dystrophy highly differs between countries. According to a report from Germany (21.2%)[6] and from the USA (23.2%)[4], Fuchs' dystrophy was the second main PKP indication. Other studies ranked Fuchs' dystrophy from the USA (10.8%)[25] as fourth and from Asia (4.5%)[33] as fifth principal PKP indication. In Europe, in Great Britain (13.5%)[24] Fuchs' dystrophy was the third main PKP indication.

There was a female preponderance (70.4%) in the Fuchs' dystrophy group, and the mean patient age (68.4±11.6y) was higher in this group as in other groups, which is in agreement with studies from North America[4,34].

The seventh most common diagnosis was corneal dystrophy other than Fuchs' in 46 cases (2.7%). We found lattice corneal dystrophy in 22 (47.83%), macular corneal dystrophy in 14 (30.43%) and granular corneal dystrophy in 10 (21.74%) cases (Figure 3). Most interestingly, the incidence of lattice corneal dystrophy was the highest between these dystrophy types in our country.

Through introduction of DSAEK and DMEK, the percentage of failed endothelial grafts did not change from 2006-2012 to 2013-2017 in our Institution, which probably shows the success of the introduced surgical techniques.

The major limitation of our study is the retrospective design, with limited availability of histopathological results, which could result in bias, over- or underestimation of the observed trends.

In conclusion, pseudophakic or aphakic bullous keratopathy is the leading PKP indication at Semmelweis University, pursued by regraft and acute necrotizing and ulcerative keratitis. In 2009, introduction of posterior lamellar keratoplasty techniques did not change this order. Advancement in corneal banking and a better referral system of patients to corneal subspecialty centers should change this order the next decades in Hungary.

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