

# Corneal Graft Rejection: Incidence and Risk Factors

Alireza Baradaran-Rafii, MD; Farid Karimian, MD; Mohammad-Ali Javadi, MD; Mohammad-Reza Jafarinasab, MD; Kiumars Nowroozpour, MD; Mojtaba Hosseini, MD; Arash Anisian, MD

*Shaheed Beheshti Medical University, Tehran, Iran*

**Purpose:** To determine the incidence and risk factors of late corneal graft rejection after penetrating keratoplasty (PKP).

**Methods:** Records of all patients who had undergone PKP from 2002 to 2004 without immunosuppressive therapy other than systemic steroids and with at least one year of follow up were reviewed. The role of possible risk factors such as demographic factors, other host factors, donor factors, indications for PKP as well as type of rejection were evaluated.

**Results:** During the study period, 295 PKPs were performed on 286 patients (176 male, 110 female). Mean age at the time of keratoplasty was  $38\pm 20$  (range, 40 days to 90) years and mean follow up period was  $20\pm 10$  (range 12-43) months. Graft rejection occurred in 94 eyes (31.8%) at an average of  $7.3\pm 6$  months (range, 20 days to 39 months) after PKP. The most common type of rejection was endothelial (20.7%). Corneal vascularization, regrafting, anterior synechiae, irritating sutures, active inflammation, additional anterior segment procedures, history of trauma, uncontrolled glaucoma, prior graft rejection, recurrence of herpetic infection and eccentric grafting increased the rate of rejection. Patient age, donor size and bilateral transplantation had no significant influence on graft rejection.

**Conclusion:** Significant risk factors for corneal graft rejection include corneal vascularization, anterior synechiae, irritating sutures, active inflammation, regrafting, additional surgery, trauma, uncontrolled intraocular pressure, history of graft rejection, recurrent herpetic infection, eccentric grafting and corneal scarring. Recipient age and donor cornea size do not seem to be risk factors for corneal graft rejection.

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**Correspondence to:** Alireza Baradaran-Rafii, MD. Assistant Professor of Ophthalmology; Ophthalmic Research Center, Labbafinejad Medical Center, Boostan 9 St., Pasdaran Ave., Tehran 16666, Iran; Tel: +98 21 22585952, Fax: +98 21 22590607, e-mail: alirbr@gmail.com

## INTRODUCTION

Penetrating keratoplasty (PKP) is the most common solid tissue transplantation in humans.<sup>1</sup> In the year 2000, more than 2100 corneas provided by the Eye Bank of I.R. Iran were trans-

planted.<sup>2</sup> Recent advances in surgical technique, operating microscopes, suture materials and cornea preservation together with the use of steroids and immunosuppressive agents, have greatly improved the success rate of corneal transplants.<sup>1,3</sup>

Despite these advances, rejection of the donor endothelium is the leading cause of corneal transplant failure.<sup>3-5</sup> The reported incidence of corneal graft rejection varies from 2.3% to 68% in different studies.<sup>6,7</sup> At least one episode of rejection may occur in 30% of grafts overall, 12% of low-risk grafts and 40% of high-risk grafts, eventually leading to complete loss of corneal transparency. Rejection most commonly occurs 4 to 18 months following transplantation, but may be seen any time after surgery. In one report, 53.3% of rejections occurred during the first year after transplantation.<sup>6</sup>

Various risk factors for graft rejection have been reported including loose sutures, early suture removal,<sup>8</sup> extent and severity of recipient corneal vascularization,<sup>3,8</sup> increasing number of regrafts,<sup>8,9</sup> bilateral grafts,<sup>9,10</sup> anterior synechiae,<sup>11</sup> ocular inflammation, younger recipient age,<sup>8</sup> size of donor cornea,<sup>10,11</sup> graft eccentricity, uncontrolled glaucoma,<sup>12</sup> atopic dermatitis and dry eye states.<sup>13,14</sup>

Considering the importance of graft rejection and the subsequent risk of failure, this study was planned to determine the incidence of corneal graft rejection and factors influencing its rate at our institute.

## METHODS

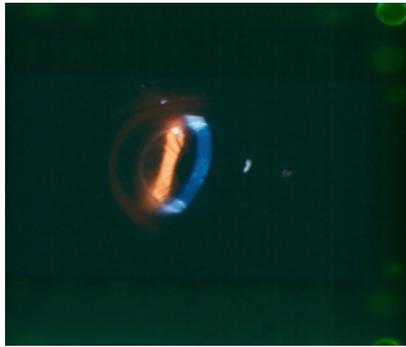
Hospital records of all patients who had undergone corneal transplantation from January 2002 to January 2005 with at least one year of follow up were reviewed. Patients who received immunosuppressive therapy other than systemic steroids were excluded. All clinical data before and after PKP were collected. In patients with rejection, the type of rejection, possible risk factors, method and result of treatment and final corneal transparency were evaluated.

All procedures were performed by two of the authors (F.K., M.A.J.) under general anesthesia. Donor corneas were harvested either from fresh whole globes, preserved in cold wet chambers or corneoscleral rims preserved in media (Optisol GS, Bausch & Lomb, USA). The Barron-Hessburg vacuum trephine (Katena, USA) was used to cut the corneas. Donor-

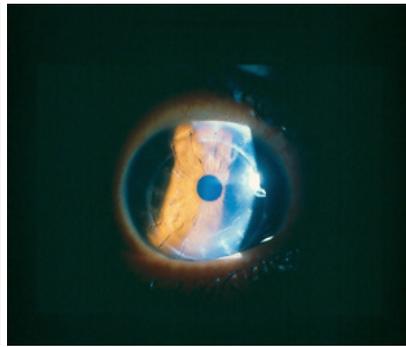
recipient disparity was 0.25-0.5 mm. Grafts were sutured with 10-0 nylon (CU-1, Alcon laboratories, USA) using interrupted, single running or combined sutures based on surgeon's judgment. Postoperatively, topical betamethasone 0.1% drops were started from the day after surgery every 6 hours, continued for 6-8 weeks and tapered according to anterior chamber and/or ocular surface inflammation. In cases with no inflammation, topical steroids were tapered off over 8 weeks. In cases with severe corneal or anterior chamber inflammation, oral prednisolone (1-2 mg/kg for 7-10 days) was also administered. Follow up visits were scheduled on days 1, 2 and 3, weekly up to one month, every two weeks up to three months, monthly up to one year and every 3-4 months, thereafter.

Prerequisites for the diagnosis of graft rejection included corneal transparency and absence of any sign of rejection during the first 10 postoperative days. Graft rejection was diagnosed based on biomicroscopic findings. Epithelial rejection was defined in the presence of an epithelial line that stained with fluorescein and changed on sequential visits. Subepithelial infiltration was defined as multifocal infiltrative lesions with no other inflammatory signs in the superficial stroma (Fig. 1). Local endothelial rejection was diagnosed in the presence of white keratic precipitates (KPs) in a limited area of the donor corneal endothelium with or without mild anterior chamber reaction. Diffuse endothelial rejection was defined in the presence of an endothelial rejection line (Khodadoust line), and/or diffuse KPs with or without corneal edema (Figures 2 and 3).

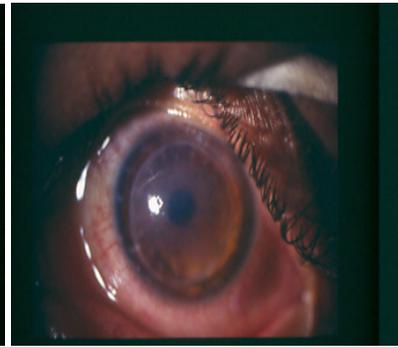
Epithelial and subepithelial rejections were treated with topical betamethasone 0.1% drops 4-6 times per day with gradual tapering. In milder forms of endothelial rejection, betamethasone eye drops were initiated on a more frequent basis (every 1 hr). In severe cases, oral prednisolone 1-2 mg/kg was added. When there was no sign of improvement despite frequent steroid treatment for three days, a subtenon injection of methylprednisolone (40 mg) was given.



**Figure1** Multiple subepithelial infiltrations



**Figure2** Endothelial rejection with Khodadoust line



**Figure 3** Endothelial rejection with diffuse corneal edema

Based on biomicroscopic and retinoscopic findings, grafts were classified as clear, hazy, and opaque. If the cornea was free of edema or opacity such that iris and anterior chamber details were clearly visible and the eye was easily refractable, the graft was considered clear. In the presence of corneal edema or opacity such that iris and anterior chamber details were not clearly visible and the eye was barely refractable, the graft was considered hazy. If corneal edema was so severe that iris and anterior chamber details were barely visible and refraction was impossible, the graft was considered opaque. Hazy and opaque corneas despite appropriate medical therapy were considered as failed grafts.

Multivariate logistic regression was used to evaluate the significance of possible risk factors.

## RESULTS

Data related to 295 corneal transplantations in 286 patients including 176 male and 110 female subjects were reviewed. Mean age at the time of surgery was  $37 \pm 20$  (range, 40 days to 90) years and mean follow up period was  $20 \pm 10$  (range 12-43) months. The most common indications for PKP in descending order included keratoconus (31.9%), regrant (13.9%), infectious keratitis (12.6%), traumatic scars (3.7%) and sequelae of chemical burns (2%). PKP was optical in 235 (79.7%), tectonic in 47 (15.9%) and therapeutic in 13 (4.4%) of the eyes. Donor

corneas were provided either from whole globes (71.9%) or corneoscleral rims (28.1%) with mean preservation time of  $2 \pm 1.9$  (range 1-6) days.

At final follow up, 70.6% of corneas were clear. The rates of graft clarity for different indications of PKP were as follows: congenital hereditary endothelial dystrophy, 100%; keratoconus, 97.8%; corneal dystrophies, 96.3%; pseudophakic bullous keratopathy, 66.7%; aphakic bullous keratopathy, 61.5%; vascularized corneal scars, 60%; re-grafts, 47%; traumatic corneal scars, 28% and chemical burns, 16.7%. Rejection was observed in 93 grafts (31.5%) which occurred once in 61 (20.7%), twice in 23 (7.8%), three times in six (2%) and more than three times in three (1%) eyes.

The first rejection episode occurred at an average duration of  $7.3 \pm 6$  months (range, 20 days to 39 months) after PKP. Rejections occurred within the first six months in 59 (63.4%) and within one year in 81 (87.1%) of 93 cases. Endothelial rejection was the most common type (61 eyes, 20.7%) followed by subepithelial (9 eyes, 3.1%) and stromal infiltrates (5 eyes, 1.7%). All corneal layers were involved in 18 (6.1%) eyes with rejection. No correlation existed between duration of preservation and rejection. Graft failure occurred in 73 (24.8%) eyes which was due to rejection in 18 (6.1%), early decompensation in 21 (7.1%) and late decompensation in 34 (11.5%) eyes.

Table 1 summarizes possible risk factors for rejection. Rejection occurred in 40 of 140

(28.6%) patients aged less than 40 and in 55 of 146 (37.7%) older patients ( $P=0.95$ ). However, there was a positive correlation between age and corneal transparency ( $P<0.001$ ); older patients had a higher chance of a clear graft.

Pre-existing corneal vascularization was present in 86 (29.2%) eyes. Rejection occurred in 27.8% of eyes without vascularization vs 38.9%, 48.3% and 38.5% of eyes with mild, moderate and severe vascularization, respectively ( $P=0.15$ ). At final follow up, 78.9% of corneas without vascularization were clear, however 77.8%, 62.1% and 30.8% of corneas with mild, moderate and severe vascularization remained clear, respectively. Graft failure due to rejection occurred in 4.8% of eyes in the non-vascularized group vs 13.8% of vascularized eyes which was proportionate to the extent of vascularization ( $P<0.001$ ).

Rejection occurred in 18 of 37 (48.7%) re-grafts compared to 76 of 258 (29.5%) primary grafts ( $P=0.025$ ). Corneas remained clear in 17 (47%) re-grafts vs 190 (73.8%) primary grafts ( $P=0.25$ ). Failure occurred in 18.8% and 4.6% of re-grafts and primary grafts respectively ( $P<0.001$ ).

Fifty-two eyes (17.5%) underwent PKP as a second eye graft (i.e. bilateral graft). Rejection rate was 27.5% and 32.8% in unilateral and bilateral grafts, respectively ( $P=0.035$ ). At the end of follow up, 98% of bilateral and 65.2% of unilateral cases had clear grafts ( $P<0.001$ ). Failure rate in the unilateral group was 7.4%, but no case of failure occurred in the bilateral group ( $P<0.001$ ). In the keratoconus subgroup ( $n=94$ ), there were 10 (10.6%) cases of graft rejection in unilateral cases vs 8 (8.5%) in bilateral grafts ( $P>0.5$ ).

Donor size was  $>8$  mm in 110 cases (37.3%) and  $\leq 8$  mm in 185 cases (62.7%). Failure rate was 6.0% in cases with donor  $>8$  mm vs 6.3% in cases with donor  $\leq 8$  mm ( $P=0.11$ ). At final follow up, 81 eyes (73.6%) of the former group and 129 eyes (69.7%) of the latter group had clear grafts ( $P>0.5$ ).

Iridocorneal adhesion was present in 34 cases (11.5%). At the end of follow up, 15 eyes (44.1%) with and 194 eyes (74.3%) without

anterior synechiae had clear grafts ( $P=0.005$ ). Failure rate due to rejection was 49.2% vs 20.6% in eyes with and without anterior synechiae, respectively ( $P<0.005$ ).

Loose or broken sutures were present in 21 eyes (7.1%). Rejection rate was 78.3% vs 28.1% in eyes with and without these irritating sutures ( $P<0.001$ ).

Active inflammation of the cornea or anterior segment was present in 30 cases (10.2%) at the time of surgery which led to graft rejection in 36.7% of these eyes compared to 19% in eyes without inflammation ( $P=0.0035$ ). Clear grafts were present in 9 (30%) vs 200 (75.5%) eyes and the rate of failure due to rejection was 20% vs 4.5% in eyes with and without inflammation, respectively ( $P<0.001$ ).

Intraocular procedures other than PKP were performed in 30 (10.2%) cases simultaneously or sequentially. The rate of rejection was 50% in this group compared to 12% in other cases ( $P=0.025$ ). At final follow up, the graft remained clear in 57.1% vs 72.3% of eyes with and without additional procedures ( $P=0.002$ ).

Traumatic scars were the indication for corneal graft in 11 eyes (3.7%), of which 63.6% developed graft rejection which was higher than other indications ( $P=0.02$ ). At the end of follow up, 28.6% of the grafts remained clear in cases with traumatic scars. Failure rate due to rejection was 14.3% in this group.

Fifteen eyes (5.1%) had glaucoma pre-operatively, of which 60% (9 eyes) developed graft rejection ( $P=0.02$ ). Finally two grafts (13.3%) remained clear and 13 failed, of which one case (7.7%) was due to rejection ( $P>0.05$ ).

Nine cases (3.1%) had eccentric grafts. Rejection rate was 66.7% in this group compared to 30.7% in those with a central graft ( $P=0.038$ ).

Thirteen cases (4.4%) had history of graft rejection in the same or fellow eye, of which 69.2% developed rejection ( $P=0.002$ ). Failure due to rejection was seen in 15.4% of these cases ( $P=0.001$ ). Rates of corneal clarity were not significantly different between eyes with or without such history.

Bacterial keratitis occurred in five cases (1.7%), two of which experienced graft rejection (P=0.02). Rates of clear cornea and failure due to rejection were 60% and 20%, respectively.

Nine eyes (3.1%) had herpetic recurrence

on the graft, of which 66.7% developed graft rejections (P=0.021).

One eye underwent Nd:YAG laser posterior capsulotomy and had clear graft during the follow up period.

**Table 1** Risk factors for graft rejection

Risk factors	No. (%) of eyes	Graft rejection (%)	P value	Corneal transparency (%)	Failure due to rejection (%)	P Value
Age						
< 40 yrs	183 (62)	28.6	0.95			
≥ 40 yrs	112 (38)	37.7				
Corneal vascularization						
Mild	18 (6.1)	38.9	0.015	77.8	13.8	<0.001
Moderate	29 (9.8)	48.3		62.1		
Severe	39 (13.2)	38.5		30.8		
Without	209 (70.9)	27.8		78.9		
Regraft	37 (12.5)	48.7	0.025	47	18.8	<0.001
Primary graft	258 (87.5)	29.5		73.8	4.6	
Graft in second eye	52 (17.6)	27.5	0.035	98	7.4	<0.001
Unilateral graft	243 (82.4)	32.8		65.2		
Size of donor cornea						
≤ 8 mm	185 (62.7)	30.5	0.3	69.7	6.3	0.11
> 8 mm	110 (37.3)	29.8		73.6	6	
Active intraocular inflammation	30 (10.2)	36.7	0.035	30	20	<0.001
Secondary intraocular surgery	30 (10.2)	50	0.025	57.1		
Irritating suture	21 (7.1%)	78.3	<0.001			
Iridocorneal adhesion	34 (11.5%)	64.7	<0.001	44.1	49.2	0.005
Uncontrolled intraocular pressure	15 (5.1)	60	0.02	13.3	7.7	0.1
History of graft rejection	13 (4.4)	69.2	0.002	29.2	15.4	0.001
Traumatic scar	11 (3.7)	63.6	0.02	28.6	14.3	<0.001
Eccentric graft	9 (3.1)	66.7	0.038			
Recurrence of herpes simplex	9 (3.1)	66.7	0.021			
Ulcer in corneal graft	5 (1.7)	40	0.021	60	20	0.001

- Chi square test

## DISCUSSION

The most common type of rejection in our study was endothelial with an incidence of 20.7%. Other series have reported endothelial rejection in 12% to 44% of eyes undergoing PKP.<sup>7,15,16</sup> Variations of these rates may be due to differences in patient population, indications for PKP, diagnostic criteria for rejection, and immunosuppressive regimens. In our series,

subepithelial infiltrations were observed in 3.1% of cases, which has been reported from 2.4% to 2.8% in other studies.<sup>3,15</sup> This type of rejection may be diagnosed less often due to the transient nature of the infiltrates and minimal effect on visual acuity.

It has been postulated that acute rejection is less common in older patients due to both immunosenescence and decreased resistance to immunosuppressive drugs.<sup>17</sup> We found no

difference in rejection rates in patients younger or older than age 40, which is the same as the findings of Vail<sup>18</sup> and Maguire.<sup>12</sup> The former investigator did not find age to be a risk factor for rejection. Conversely, some reports have suggested age over 40 to be a risk factor for rejection and graft failure.<sup>11,19</sup> The patients in the current study were relatively young because keratoconus was the most common indication for PKP. However in most other studies, bullous keratopathy in older patients has been the most common indication for PKP. Therefore it is difficult to judge and compare any possible correlation between age and rejection rates.

We observed a direct correlation between the extent and severity of corneal vascularization and graft rejection. Aldredge and Krachmer<sup>7</sup> found that vascularization increases endothelial rejection rate but not subepithelial infiltrates and epithelial rejection. In reports by Yamagami<sup>20</sup> and Koay et al<sup>21</sup> there was a positive correlation between rejection and the extent of vascularization: severe vascularization in all four quadrants of the recipient cornea increased the risk of graft failure by 1.7 times compared to a non-vascularized recipient cornea.<sup>12</sup> The underlying cause of vascularization in the recipient cornea may by itself predispose to rejection and adversely affect graft survival.<sup>21</sup> More widespread use of immunosuppressive agents in high risk patients has improved the survival of re-grafts. In Maguire's study,<sup>12</sup> the risk of rejection and failure after re-grafts was three times higher than primary grafts. Immune system sensitization is increased following each corneal allograft which in turn accelerates immune reactions and graft rejection. HLA matching has been suggested to improve graft survival in normal-risk PKPs.<sup>22</sup> In our study, previous graft rejection was a risk factor for rejection and subsequent failure; however we could not find any significant correlation between this factor and graft failure overall. Maguire et al<sup>12</sup> found sequential corneal grafts to be associated with an increased risk of rejection and subsequent failure. Due to sensitization of the recipient's

immune system, especially against HLA class 2 antigens, corneal re-grafts can cause new attacks of rejection.<sup>8,11</sup> Prolonged use of low dose topical steroids can suppress the local immune system and prevent recurrence of rejection.<sup>23</sup>

Overall, second eye grafts had a better prognosis in our series; there were less rejection-induced graft failures and more durable clear grafts in second eyes. According to Musch et al<sup>9</sup> the rate of rejection in the second eye was the same as the first eye, one and five years postoperatively. The risk of rejection in the second eye is not increased if there has been no rejection in the first eye, however the opposite may hold true in cases with rejection in the first eye. In patients with keratoconus, rejection rates were similar in unilateral and bilateral grafts.<sup>2</sup> Tuft et al<sup>10</sup> also reported no association between bilateral grafting and graft survival. Conversely, Donshik et al<sup>24</sup> reported a rejection rate of 27% in bilateral vs 13% in unilateral cases.

Donor size had no effect on graft rejection and subsequent failure. Some studies have reported donor corneas larger than 7.5 mm as a risk factor for graft rejection.<sup>10,14</sup> Reinhard et al<sup>22</sup> have reported larger sized donors as a risk factor for rejection but at lower chance for failure. Trigui et al<sup>11</sup> also showed an increased rejection rate with corneal grafts  $\geq 8$  mm in size. Conversely in the Collaborative Corneal Transplantation Studies (CCTS), graft size less than 8 mm was at greater risk of rejection.<sup>12</sup> Due to a larger number of Langerhans cells and their proximity to limbal vessels, a larger donor cornea may increase the risk of rejection.<sup>15,24</sup> In the CCTS, surgeons were free to choose different graft sizes and suturing methods. Therefore, smaller grafts with interrupted sutures were used in high-risk cases and the study was confounded by the indication for PKP.<sup>12</sup> It seems that the indication for PKP was of greater relevance than graft size, which actually was a secondary issue.

Our study showed that high IOP is a risk factor for corneal graft rejection, but not subsequent failure. Conversely, the CCTS reported elevated IOP as a risk factor for graft failure but

not for rejection.<sup>12</sup> Yamagami et al<sup>20</sup> reported coexistence of glaucoma and anterior synechiae as a major risk factor for rejection. According to Naache et al,<sup>25</sup> reversibility of graft rejection is the same in eyes with and without glaucoma or ocular hypertension. Several studies have reported the presence of anterior synechiae to be a risk factor for glaucoma as well as graft rejection and failure. This may be due to easier access of blood vessels to donor endothelial cells.<sup>12,15,18,22</sup> Our results are consistent with those studies.

In the current series, irritating sutures and anterior segment inflammation were associated with graft rejection. These factors predispose to presentation of class 2 HLA antigens leading to graft rejection.<sup>15</sup> Additionally, in the present study concomitant anterior segment procedures at the time of transplantation were associated with a higher rate of rejection and lower graft survival. In the CCTS, simultaneous anterior segment surgery had a strong correlation with the rate of graft rejection and corneal transparency.<sup>8,12</sup> The effect of prior anterior segment surgery on graft rejection and failure is not well known, however it has been introduced as a risk factor for rejection in Australia.<sup>26</sup>

Eccentric grafting, history of trauma, re-activation of herpetic keratitis on the graft and history of chemical burns were other risk factors for graft rejection in our study. PKP in eyes with history of chemical burn should be considered a high-risk graft.<sup>6,14,15</sup> Prior herpetic keratitis and the resultant corneal vascularization can act as precipitating factors for graft rejection and subsequent failure.<sup>12,15,18,23</sup>

In conclusion, risk factors for corneal rejection and probably subsequent failure include recipient vascularization, regrafts, anterior synechiae, irritating sutures, anterior segment inflammation, simultaneous anterior segment surgery, eccentric grafts, history of trauma (particularly chemical burns), previous history of rejection, recurrence of herpetic keratitis and elevated IOP. Our study did not demonstrate recipient age and donor size to be risk factors for corneal graft rejection.

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