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Title: Gender matching did not affect 2-year rejection or failure rates following DSAEK for Fuchs endothelial corneal dystrophy

Short title: Gender and H-Y matching in DSAEK

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Disclosure

None of the authors have any potential conflict of interest

Abstract

Purpose*:* To investigate if donor to recipient gender or H-Y mismatching was associated with graft rejection or failure following Descemet stripping automated endothelial keratoplasty (DSAEK) in patients with Fuchs endothelial corneal dystrophy (FECD).

Design*:* Clinical Cohort study.

Methods*:* We used multi-center registry including patients older than 18 years who had undergone their first DSAEK for FECD between January 2008 and March 2018. The impact of donor and recipient gender incompatibility (including H-Y mismatches) on corneal graft rejection and failure was evaluated using Kaplan–Meier curves and univariable and multivariable Cox models.

Results*:* Outcome data from 4341 eyes (3915 from the UK and 426 from Italy) were analyzed. Graft failure at 2-year follow-up occurred in 477 (11.0%) cases. Graft rejection at 2-year follow-up occurred in 175 cases (4.0%); 58 (1.3%) of whom developed graft

failure. There was no significant effect of gender or H-Y mismatching on either rejection (p=0.12, p=0.06) or failure (p=0.28, p=0.14), respectively.

Conclusions*:* In patients with FECD undergoing DSAEK, we found no significant influence of gender and or H-Y mismatch on graft rejection or failure.

Introduction

Gender and H-Y mismatching has been shown to influence graft survival in eyes that underwent penetrating keratoplasty (PK) for Fuchs endothelial corneal dystrophy (FECD).[1-4] Encoded by the Y chromosome and restricted by HLA-A*0201, the H-Y antigen can only be found in A1 positive males. Based on data from the United Kingdom (UK) transplant registry, H-Y mismatching defined as corneal transplantation from a male donor to female recipient, may be a significant risk factor for graft rejection after PK. Additionally, in a series of 4314 PKs performed for FECD, Hopkinson et al., reported that the 5-year cumulative survival of presumed H-Y mismatched penetrating grafts was significantly lower compared to that of matched transplants.[2] Similarly, Böhringer et al. observed a lower rate of rejection-free graft survival in H-Y mismatched penetrating grafts.[1] Recently, Kim et al. also found that H-Y matching for PK was associated with lower probabilities of graft rejection even in high-risk conditions.[5]

Currently, endothelial keratoplasty (EK) including Descemet stripping automated endothelial keratoplasty (DSAEK) and and Descemet membrane endothelial keratoplasty (DMEK) has replaced PK as the preferred surgical treatment for FECD. Although the risk of graft rejection is lower following EK than PK, minimising graft rejection is still crucial to optimize graft survival. Whether there is an effect of gender and H-Y mismatch on graft rejection and survival for patients undergoing EK, however, remains unclear, principally because most studies are based on limited sample sizes, which reduce the probability of detecting a true difference. [2, 6, 7] The purpose of the current study, therefore, was to

investigate whether gender mismatch and presumed H-Y mismatching was associated with graft survival and rejection following DSAEK for FECD.

Methods

A cohort study using data from a multi-center registry was conducted to determine the impact of donor and recipient gender incompatibility (including H-Y mismatches) on corneal graft rejection and failure. Data were obtained from the UK NHS Blood and Transplant national database and the Fondazione Banca degli Occhi del Veneto Onlus registry (Italy). The study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board.

Inclusion criteria were adult patients aged 18 years or older who had undergone a primary DSAEK for FECD between January 2008 and March 2018. Eyes with a history of keratoplasty were excluded. In patients that underwent bilateral sequential DSAEK, only the first eye was included for analysis. The outcomes were graft rejection and graft failure secondary to endothelial failure at up to 2 years after transplantation.

Criteria used to diagnose graft rejection were the presence of signs of immune-mediated rejection such as rejection line, keratic precipitates and anterior segment inflammation with or without the development of corneal edema. Graft failure from endothelial failure was defined as a cloudy cornea that did not clear or required a regraft at any time after surgery. Diagnoses of graft rejection and failure were made only if the graft had remained clear for at least 2 weeks after surgery. Primary graft failure and failure due to corneal infections were excluded.

Data analysis

Statistical analyses were performed using STATA 16.1 (StataCorp, College Station, TX) and a $p<0.05$ was considered significant. Kaplan–Meier analysis was used to estimate cumulative probabilities while univariable and multivariable Cox proportional hazard

models were used to determine hazard ratios (HRs) and corresponding 95% confidence interval (CI) of graft rejection and failure. Factors considered in the univariable models were: donor and recipient age (19–40, 41–60, 61–75, and >75 years), donor-to-recipient gender match (male[M]-female [F], M-M, F-M, and F-F), H-Y matching and year of surgery (2008-2010, 2011-2012, 2013-2014, and 2015-2018). Additional cox regression models were fitted to assess whether an independent relationship exists with the gender and H-Y matching variables and graft rejection and failure while adjusting for independent variables, which have reached a significance level of less than 0.05 in the univariable analysis. An effect of country was noted, therefore, post-hoc analysis comparing donor and recipient characteristics and frequencies of donor-recipient combinations and H-Y mismatching was performed.

Based on the alpha error of 0.05 and power of 90%, distribution of the H-Y mismatch (36%) and a 4% rejection rate, a post-hoc sample size calculation (n=4341) was performed. The minimum detectable effect expressed as a HR was 1.11.

Results

Data from 4,341 eyes (3,915 from the UK and 426 from Italy) were analyzed. Eleven eyes were not included in the analyses since the graft failed on the day of surgery. Mean donor age was 69.4 years (standard deviation, SD: 11.6) and mean recipient age was 71.9 years (SD: 10.2). The number of male donors and recipients were 2,689 (62.1%) and 1,801 (41.6%), respectively. Graft rejection occurred in 175 cases (4.0%) and 58 (1.3%) of these resulted in graft failure. There were 477 (11.0%) cases of endothelial graft failure in the absence of any history of a rejection episode.

Matching and graft rejection

The cumulative probabilities of graft rejection at 1 and 2 years was 0.028 (0.023 to 0.038) and 0.051 (0.044 to 0.059), respectively (Figure 1). A univariable Cox model for graft rejection did not detect a significant difference among donor-recipient gender matches (p=0.118). Kaplan-Meier survival curves of the cumulative probability of graft rejection stratified by donor-recipient gender matching combinations and H-Y mismatch are shown in Figures 2 and 3

The M-F match yielded the lowest risk of rejection in univariable and multivariable analyses (Table 1). Compared with other gender matches, an M-F match was not associated with a significantly difference in rejection rate and possibly decreased this risk with significance in the multivariable model (HR=0.71 [95% CI: 0.51-0.98], p=0.040). The risk of graft rejection was lower in older recipients in both univariable (0.77 [0.67-0.89], p<0.001) and multivariable models including either gender matching or H-Y mismatch (0.78 [0.68-0.90], p=0.001). No significant association with the year of surgery was found (p-value from global test=0.794). Graft rejection was more common in patients in Italy compared to those in the UK (HR 1.77 [1.14-2.76], p-value=0.011) (Table 1).

Matching and graft failure

The cumulative probabilities of graft failure at 1 and 2 years were 0.097 (0.088 to 0.106) and 0.136 (0.125 to 0.147), respectively (Figure 1). Kaplan-Meier survival curves stratified by donor-recipient gender combinations and H-Y mismatch are shown in Figures 4 and 5. There were no significant effects of gender (p=0.281) or H-Y (p=0.144) mismatching.

In the univariable Cox model, there was an increased risk of failure when transplanting corneas from older donors (1.10 [1.01-1.18], p=0.020); but this was not significant in the multivariable models (Table 1). Treatment year (as quartiles) was associated with graft failure (p<0.001). Significantly lower chances of graft survival following DSAEK were recorded in the years 2011-2012 compared to years 2015-2018 (0.61 [0.48-0.80], p<0.001), and the association remained significant in multivariable models (Table 1).

Differences between countries

Graft failure was higher in patients in the UK compared to Italy (0.33 [0.20-0.54], p<0.001) while rejection was higher in Italy (1.77 [1.14-2.76], p=0.01) in both univariable and multivariable models. Given the effect of country on both graft rejection and failure,

analyses comparing baseline characteristics between UK and Italy were performed. UK donors were on average 9 years older ($p<0.001$) and recipients were slightly younger ($p<0.001$) than their Italian counterparts. Differences in gender matching between the UK and Italy are highlighted in supplementary table 1 and 2. Compared to univariable models, differences between Italy and the UK were substantially unchanged in the multivariable models (Tables 1).

Discussion

Results from our study show that, in contrast to the findings for penetrating grafts [1-4,8,5], there is no apparent role of donor-recipient gender and H-Y mismatch in increasing the risk of graft rejection and failure following DSAEK. This finding is in agreement with previous studies on the role of gender matching in DSAEK which concluded that neither the H-Y matching nor the donor-recipient gender matching had an effect on graft survival and failure.[2, 6] Moreover, our study was powered adequately to detect a minimal HR difference of 1.11.

In a registry study, Hopkinson et al. reported that H-Y donor recipient mismatch in patients undergoing a DSAEK was not associated with reduced graft survival.[2] Similarly, in a retrospective study in 2018, Price et al. showed that neither gender nor H-Y mismatch affected the 5-year graft survival and rejection rates following DSAEK or DMEK for FECD.[6] The difference in the effects of H-Y mismatch and gender matching on graft survival and rejection between PK and DSAEK in patients with FECD might be associated with the immunological advantages of EK over PK. In DSAEK, the graft is inserted into the anterior chamber with less direct exposure to antigen presenting cells in the cornea or ocular surface. DSAEK also avoids suture-related inflammation. In vascularized recipient corneas, there is less contact with vessels in the recipient stroma, leading to reduced immune cell trafficking. More importantly, the DSAEK graft is associated with less immunogenicity due to a reduced amount of stromal tissue.[9] Graft rejection rates following endothelial keratoplasty (DSAEK and DMEK) are also lower than PK and these combined advantages may help explain the lack of an effect of gender and H-Y mismatch on graft rejection and graft survival following DSAEK. It is also reasonable to think that the mechanisms of anterior chamber-associated immune deviation (ACAID), which essentially contribute to the immune privilege of the eye, might also play a role. In ACAID, histocompatibility antigens injected into the anterior chamber actively produce systemic

tolerance.[10-12] Whether ACAID contributes to the lower rates of graft rejection following DSAEK compared to PK, however, is currently unknown.[13]

It has been reported that recipient and donor age are associated with DSAEK rejection and failure with younger patients experiencing more frequent rejection episodes[14, 15] and older donor corneas being associated with higher rates of graft failure.[16] An unexpected finding of our study was the higher rate of graft failure in UK (13.15%) compared to Italy (4.69%) but the lower rejection rate following DSAEK performed in UK. The reasons for this are not clear, but may reflect differences in measured variables, such as donor age, or in potential unmeasured confounders, e.g. endothelial cell density (ECD) and post-mortem times. The average donor age was 61.6 years in Italy compared to 70.2 years in the UK and times from death to corneoscleral disc excision are lower in Italy (mean 12.23±6.28 hours, unpublished data) compared to the UK (31.4±9.6 hours)[17]. A previous study in the UK by Armitage et al. did not report any significant effect of donor age or post-mortem time on graft survival but was limited by a comparatively smaller number of younger donors and a small number of donors with short post-mortem times. Any apparent lack of an effect is restricted to an older donor age range and long post-mortem times. It is clear, therefore, that further studies are needed to address this point.

In our study, we included in the analysis the year of transplantation. This was to take into account the change in graft preparation methods that we have witnessed in the past years, from manual donor dissection, to surgeon and then eye-bank microkeratome dissection as well as the current ultra-thin eye-bank prepared DSAEK tissues.[18] The year of surgery had no effect on graft rejection rate, however, it was shown to have a role in graft failure, with reduced risk of failure for grafts performed in the years 2011-2012 and 2013-2014 compared to 2008-2010. It is unclear, however, why this trend was not supported by the results from the last timeframe 2015-2018, that showed no difference in graft failure compared to 2008-2010.

A limitation of our study is the absence of information on the HLA type of donors which, due to the HLA-A1 restriction of the H-Y antigen, does not allow us to exactly quantify how many of the male-to-female donor corneas were effectively H-Y mismatched. More than 50% of EKs analyzed in our study, however, were donor/recipient gender mismatched and almost 35% were presumed H-Y mismatched, which was due to the disparity resulting from a higher percentage of male corneal donors (62%) and the higher prevalence of FECD in female patients.[19] It is reasonable to conclude that the latter together with our large sample sizes, overcame this limitation.

Overall, our results indicate that as opposed to PK donor-recipient gender matching and H-Y matching may not be necessary in the allocation of donor corneas for DSAEK.

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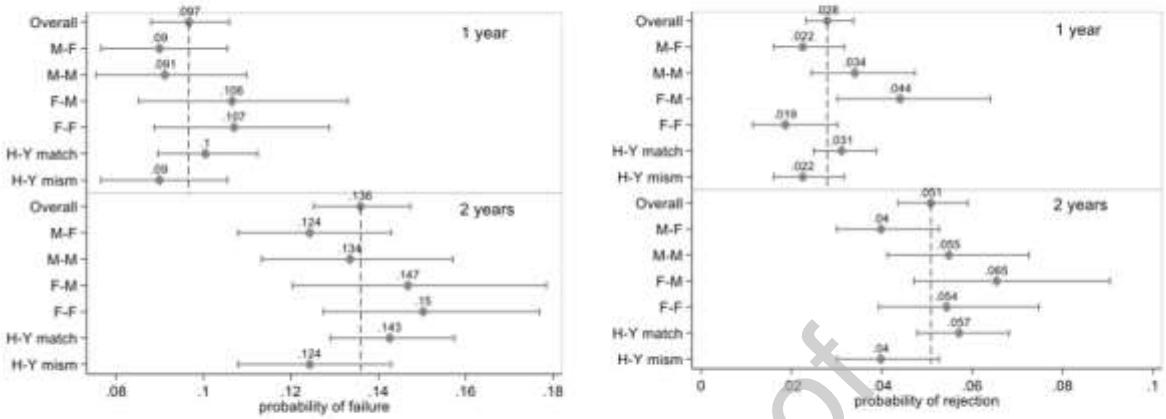

Figure 1. Forest plot representing the probability of graft failure (A) and graft rejection (B) at 1 and 2 years according to gender and H-Y matching. M-F = Male donor – Female recipient; M-M = Male donor – Male recipient; F-M = Female donor – Female recipient; F-F = Female donor – Female recipient.

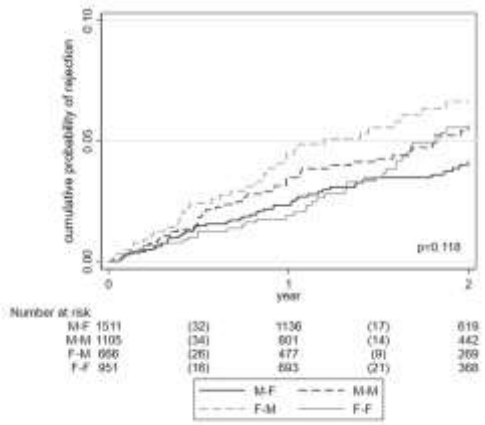

Figure 2. Kaplan-Meier survival curve showing cumulative probability of graft rejection stratified by donor-recipient gender matching combinations (p=0.118).

M-F = Male donor – Female recipient; M-M = Male donor – Male recipient; F-M = Female donor – Male recipient; F-F = Female donor – Female recipient. The rows show numbers at risk and in brackets numbers of failure at time 0, 1 and 2 years.

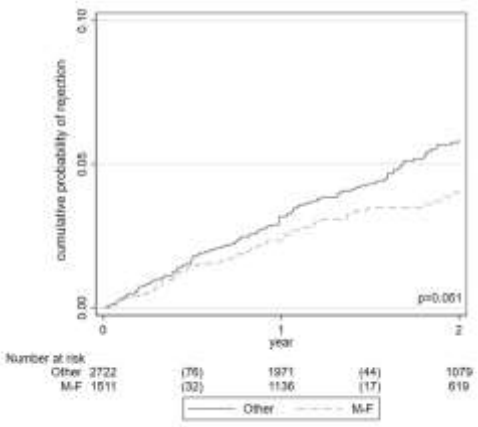

Figure 3. Kaplan-Meier survival curves showing cumulative probability of graft rejection of H-Y matched versus H-Y mismatched pairs (p=0.056).

M-F = Male donor – Female recipient; Others include: M-M = Male donor – Male recipient F-M = Female donor – Male recipient, and F-F = Female donor – Female recipient. The rows show numbers at risk and in brackets numbers of failure at time 0, 1 and 2 years.

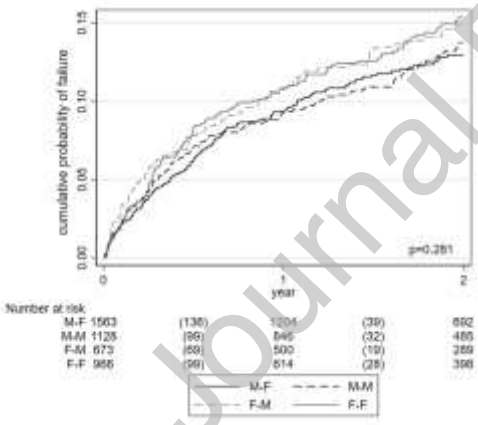

Figure 4. Kaplan-Meier survival curves showing cumulative probability of graft failure stratified by donor-recipient gender matching combinations (p=0.281).

M-F = Male donor – Female recipient; M-M = Male donor – Male recipient; F-M = Female donor – Male recipient; F-F = Female donor – Female recipient. The rows show numbers at risk and in brackets numbers of failure at time 0, 1 and 2 years.

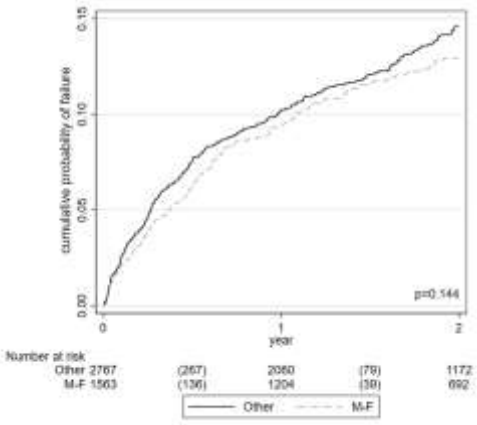

Figure 5. Kaplan-Meier survival curves showing cumulative probability of graft failure of H-Y matched versus H-Y mismatched pairs (p= 0.144). M-F = Male donor – Female recipient; Others include: M-M = Male donor – Male recipient F-M = Female donor – Male recipient, and F-F = Female donor – Female recipient. The rows show numbers at risk and in brackets numbers of failure at time 0, 1 and 2 years.

Table of Contents Statement

A two-year follow-up cohort study on 4341 eyes of patients who underwent Descemet's stripping automated endothelial keratoplasty for Fuchs endothelial corneal dystrophy did not show any effect of gender matching on graft rejection or failure

Table 1. Univariable Cox models for graft rejection and graft failure after DSAEK

	N (%) or mean ± SD	HR (95% CI)	
		Rejection	**Failure**
Gender matching			
M-F	1,563 (36.1%)	1	1
M-M	1,128 (26.1%)	1.32 (0.89-1.96)	1.05 (0.84-1.32)
F-M	673 (15.5%)	1.69 (1.10-2.58)	1.20 (0.93-1.55)
F-F	966 (22.3%)	1.21 (0.80-1.85)	1.21 (0.97-1.53)
H-Y matching grafts [#]			
H-Y matched	2,767 (63.9%)	1	1
HY mismatched	1,563 (36.1%)	0.73 (0.53-1.01)	0.87 (0.73-1.05)
Donor Age†, mean±SD	69.4 ± 11.6	0.99 (0.87-1.13)	1.10 (1.01-1.18)*
Recipient Age†, mean±SD	71.9 ± 10.2	0.77 (0.67-0.89)**	1.02 (0.94-1.12)
Country			
UK	3,904	1	1
Italy	426	1.77 (1.14-2.76)*	0.33 (0.20-0.54)**
Year			
2008-2011	1,026	1.14 (0.75-1.73)	1.08 (0.86-1.35)
2011-2012	1,018	0.94 (0.61-1.46)	0.62 (0.48-0.80)**
2013-2014	1,079	0.95 (0.62-1.48)	0.85 (0.67-1.08)
2015-2018	1,206	1	1

M-F=male donor to female recipient; M-M=male donor to male recipient; F-M=female donor to male recipient; F-F=female donor to female recipient

[#]Presumed H-Y mismatched grafts include M-F donor to recipient matched grafts. H-Y matched grafts include M-M, F-M, F-F donor to recipient matches.

†Continuous variable per 10 years

(*): p<0.05 to 0.001; (**): p<0.001

Table 2. Multivariable Cox models for graft rejection and graft failure after DSAEK (Gender matching)

	HR (95% CI)	
	Rejection	**Failure**
Gender matching		
M-F	1	1
M-M	1.32 (0.89-1.96)	1.03 (0.83-1.30)
F-M	1.76 (1.15-2.70)*	1.15 (0.89-1.59)
F-F	1.26 (0.83-1.93)	1.19 (0.94-1.49)
Donor Age†, mean±SD		1.05 (0.97-1.07)
Recipient Age†, mean±SD	0.78 (0.68-0.90)**	
Country		
UK	1	1
Italy	1.69 (1.09-2.64)*	0.36 (0.22-0.59)**
Year		
2008-2011		1.09 (0.87-1.37)
2011-2012		0.64 (0.49-0.83)**
2013-2014		0.85 (0.67-1.07)
2015-2018		1

M-F=male donor to female recipient; M-M=male donor to male recipient; F-M=female donor to male recipient; F-F=female donor to female recipient
†Continuous variable per 10 years
(*): p<0.05 to 0.001; (**): p<0.001

Table 3. Univariable and multivariable Cox models for graft rejection and graft failure after DSAEK (H-Y matching)

	HR (95% CI)	
	Rejection	**Failure**
H-Y matching grafts[#]		
H-Y matched	1	1
HY mismatched	0.71 (0.51-0.98)*	0.89 (0.75-1.07)
Donor Age†, mean±SD		1.06 (0.98-1.14)
Recipient Age†, mean±SD	0.78 (0.68-0.90)**	
Country		
UK	1	1
Italy	1.67 (1.07-2.60)*	0.36 (0.22-0.59)**
Year		
2008-2011		1.10 (0.86-1.38)
2011-2012		0.64 (0.49-0.83)**
2013-2014		0.85 (0.67-1.07)
2015-2018		1

[#]Presumed H-Y mismatched grafts include M-F donor to recipient matched grafts. H-Y matched grafts include M-M, F-M, F-F donor to recipient matches.
†Continuous variable per 10 years
(*): p<0.05 to 0.001; (**): p<0.001

Biosketch Vito Romano

Vito Romano, MD is Associate Professor of Ophthalmology at The University of Liverpool and Consultant Ophthalmic Surgeon at Liverpool University Hospitals NHS Foundation Trust where he is also Deputy Director of the Clinical Eye Research Centre. He is passionate about translational research and clinical trial design with a special interest in corneal and ocular surface diseases and ophthalmic imaging.