

# Outcomes of Descemet's membrane endothelial keratoplasty performed in combination with, before, or after cataract surgery in Fuchs' endothelial dystrophy: A review of the literature and meta-analysis

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This review aimed to compare the outcomes of Descemet's membrane endothelial keratoplasty (DMEK) in combination with (category 1), before (category 2), or after cataract surgery (category 3) in patients with Fuchs' endothelial dystrophy (FED). Primary outcome was gain in best-corrected log of minimum angle of resolution (logMAR) visual acuity (BCVA). Secondary outcomes were graft detachment, rebubbling rates, rejection, failure, and endothelial cell loss (ECL). In category 1, 2, and 3, 12 studies ( $N = 1932$ ) were included (five in category 1 [ $n = 696$ ], one in category 2 [ $n = 286$ ], and two in category 3 [ $n = 950$ ], and the remaining four compared between two of the three categories). At 6 months, the gain in BCVA was  $0.34 \pm 0.04$ ,  $0.25 \pm 0.03$ , and  $0.38 \pm 0.03$  logMAR in category 1, 2, and 3, respectively. The difference was significant between categories 1 and 2 ( $\text{Chi}^2 = 11.47$ ,  $P < 0.01$ ) and categories 2 and 3 ( $\text{Chi}^2 = 35.53$ ,  $P < 0.01$ ). At 12 months, the gain in BCVA was  $0.52 \pm 0.05$  and  $0.38 \pm 0.06$  logMAR in categories 1 & 3 ( $\text{Chi}^2 = 14.04$ ,  $P < 0.01$ ). The rebubbling rates were 15%, 4%, and 10% ( $P < 0.01$ ) and the graft detachment rates were 31%, 8%, and 13% ( $P < 0.01$ ) in categories 1, 2, and 3, respectively. However, graft rejection, survival rates, and ECL at 12 months were not different between categories 1 and 3. There is low certainty evidence that gain in BCVA in category 1 was comparable to category 3 at 6 months; however, it was significantly better with category 3 at 12 months. Although rebubbling and graft detachment rates were highest in category 1, there was no significant difference in graft rejection, survival rates, and ECL. Further high-quality studies are likely to change the effect estimate and have an impact on the confidence of the estimate.

**Key words:** Cataract surgery, DMEK, Fuchs' endothelial dystrophy, triple procedure

Descemet's membrane endothelial keratoplasty (DMEK) is considered the surgical procedure of choice for Fuchs' endothelial dystrophy (FED) and is gaining widespread acceptance over Descemet's tripping automated endothelial keratoplasty (DSAEK) for treating other endothelial diseases.<sup>[1-3]</sup> DMEK involves replacing the dysfunctional recipient corneal endothelium and Descemet's membrane with the same layers from donor cornea and offers predictable and faster visual rehabilitation with reduced risk of graft rejection relative to other keratoplasty techniques.<sup>[4-7]</sup>

FED, the leading indication for DMEK worldwide, can present with visually significant endothelial dysfunction in both phakic and pseudophakic patients.<sup>[8,9]</sup> DMEK and cataract surgery are either performed concurrently, popularly known as DMEK triple, or sequentially, wherein DMEK can be performed before (phakic DMEK) or after (pseudophakic DMEK) cataract surgery. The decision on the type of procedure can be influenced by several factors, including the extent of corneal endothelial

disease and cataract, ocular comorbidities, patient's age, other systemic comorbidities, and the surgeon's preferred surgical technique.<sup>[10,11]</sup> There are several advantages and disadvantages of each procedure; for example, phakic DMEK has the benefit of leaving patients with an accommodative advantage and the scope of correction of any refractive error with subsequent cataract surgery. However, most patients left phakic after DMEK may soon require cataract surgery, which carries the risk of graft failure.

This review aims to present the outcomes and complications of DMEK performed in combination with, before, or after cataract surgery.

## Methods

### Eligibility criteria for contributing studies for the review

**Inclusion criteria:** We selected peer-reviewed articles of human studies only and included articles in English. We reviewed

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studies in which DMEK was performed to treat FED. We included case series comparing the outcomes of DMEK performed in combination with cataract surgery versus the staged procedure.

**Exclusion criteria:** Studies including keratoplasty procedures other than DMEK or with indications other than FED and aphakic patients were excluded. However, studies with a mixed category of indications, with the most common being FED and where separate analysis was provided for FED cases, were included.

### Primary and secondary outcomes

**Primary outcome:** Mean gain in best-corrected log of minimum angle of resolution (logMAR) visual acuity (BCVA). Best-corrected logMAR visual acuity was obtained from studies and converted if not presented as logMAR. If data were presented as a median with a range, the mean was estimated according to the formula by Hozo *et al.*<sup>[12]</sup>

**Secondary outcomes:**

1. Graft detachment and rebubbling rate
2. Refractive spherical equivalent (SE) and astigmatism
3. Endothelial cell loss (ECL)
4. Graft rejection
5. Graft failure
6. Central corneal thickness (CCT)
7. Other complications: cataract surgery after phakic DMEK and glaucoma.

As studies were expected to have varying follow-ups, data were presented for the latest follow-up visit.

### Search methods for identifying studies

We performed a PubMed® search for all relevant articles using the keywords Descemet's membrane endothelial keratoplasty (DMEK), Fuchs' endothelial dystrophy (FED), cataract surgery, and DMEK triple published up to July 15, 2021.

We used Microsoft Excel 2021 spreadsheet to outline the complications and outcomes. Titles and abstracts resulting from the search were assessed by two reviewers, and full-text review of the selected abstracts was carried out. Analysis was done based on the number of eyes, and these were categorized into three categories:

Category 1: DMEK combined with cataract surgery in the same surgical sitting (DMEK triple)

Category 2: DMEK in phakic eyes or DMEK before cataract surgery (phakic DMEK)

Category 3: DMEK in pseudophakic eyes or DMEK after cataract surgery (pseudophakic DMEK).

### Statistical analysis

Mean and standard deviation were extracted for continuous data (BCVA, uncorrected visual acuity [UCVA], SE, and change in CCT). Where median and range were presented, we used Vassar Statistics employing Hozo *et al.*'s<sup>[12]</sup> technique. We used the median as the mean, where the median and interquartile ranges were presented and standard deviation (SD) as the interquartile range (IQR)/1.35. Range of data was provided as a measure of variance; this was converted to SD using the formula (maximum – minimum)/4.

Inverse variance meta-analyses were performed using Review Manager (RevMan 5.4) for continuous data such as change in BCVA and CCT. Fixed effect methods were used when there were fewer than three studies in a category. The statistical command Metaprop in Stata 17 (StataCorp 2021) was implemented to perform meta-analyses of proportion of eyes with graft detachment, rebubbling, and primary failure. Also, 95% confidence intervals (CIs) were computed using the score statistics and the exact binomial method. Freeman–Tukey double arcsine was used for transformation of proportions. A *P* value <0.05 was considered statistically significant.

## Results

Three hundred and two abstracts were screened and 12 studies were included in quantitative synthesis [Fig. 1]. These consisted of studies with either a single cohort or two cohorts – category 1 (*n* = 5), category 2 (*n* = 1), category 3 (*n* = 2), categories 1 & 3 (*n* = 2), categories 1 & 2 (*n* = 1), and categories 2 & 3 (*n* = 1) [study characteristics are summarized in Table 1]. Studies that included two categories were analyzed as separate cohorts, which resulted in eight cohorts for category 1, three cohorts for category 2, and five cohorts for category 3 eyes. This translated to a total of 1932 eyes, including 696 in category 1, 286 in category 2, and 950 in category 3.

Most of the studies were designed as retrospective case series (*n* = 10); the remainder were retrospective case–control studies (*n* = 1) and prospective case series (*n* = 1). Two studies included mixed indications; however, they were included as the authors provided separate data and analysis for FED.<sup>[13,14]</sup> Most studies had a fixed follow-up of either 6 months (*n* = 5) or 12 months (*n* = 4); others reported 2-year outcomes (*n* = 1) and 3-year outcomes (*n* = 1) or had a range of follow-up (*n* = 1; range: 3–26 months). For the two studies that also recorded 2- and 3-year outcomes, only 12 months data were recorded for analysis to ensure uniformity. Mean age was overall 67.80 years, and 67.53 ± 2.08, 56.57 ± 3.67, and 72.88 ± 2.65 years for categories 1, 2, and 3, respectively (*P* < 0.01).

### Primary outcome

*Best-corrected logMAR visual acuity*

Three studies did not provide visual acuity data; these included one category 1 study, one category 2 study, and one study including categories 1 and 3.<sup>[14–16]</sup> Out of the remaining nine, BCVA was converted from decimal to logMAR using the formula  $\log = -(\log \text{ decimal value})$  in one study.<sup>[17]</sup> Where it was presented as a median, an estimated mean was calculated.<sup>[12]</sup> Where it was reported, all studies reporting BCVA in each category reported an improvement.

Preoperative weighted mean logMAR BCVA was 0.56 SD ± 0.18, 0.29 ± 0.03, and 0.49 ± 0.08 in categories 1, 2, and 3, respectively (*P* = 0.22); this improved to 0.18 ± 0.12, 0.04 ± 0.03, and 0.12 ± 0.07 in categories 1, 2, and 3, respectively, at the latest postoperative visit.

At 6 months, there was a mean gain in logMAR BCVA of 0.34 (95% CI 0.30 to 0.38) in category 1, 0.25 (95% CI 0.22 to 0.28) in category 2, and 0.38 (95% CI 0.33 to 0.41) in category 3 [Fig. 2]. Subgroup analysis showed significant difference between categories 1 and 2 ( $\text{Chi}^2 = 11.47$ , *P* < 0.01) and between categories 2 and 3 ( $\text{Chi}^2 = 35.53$ , *P* < 0.01); however, there was no significant difference between categories 1 and 3 ( $\text{Chi}^2 = 2.20$ ,

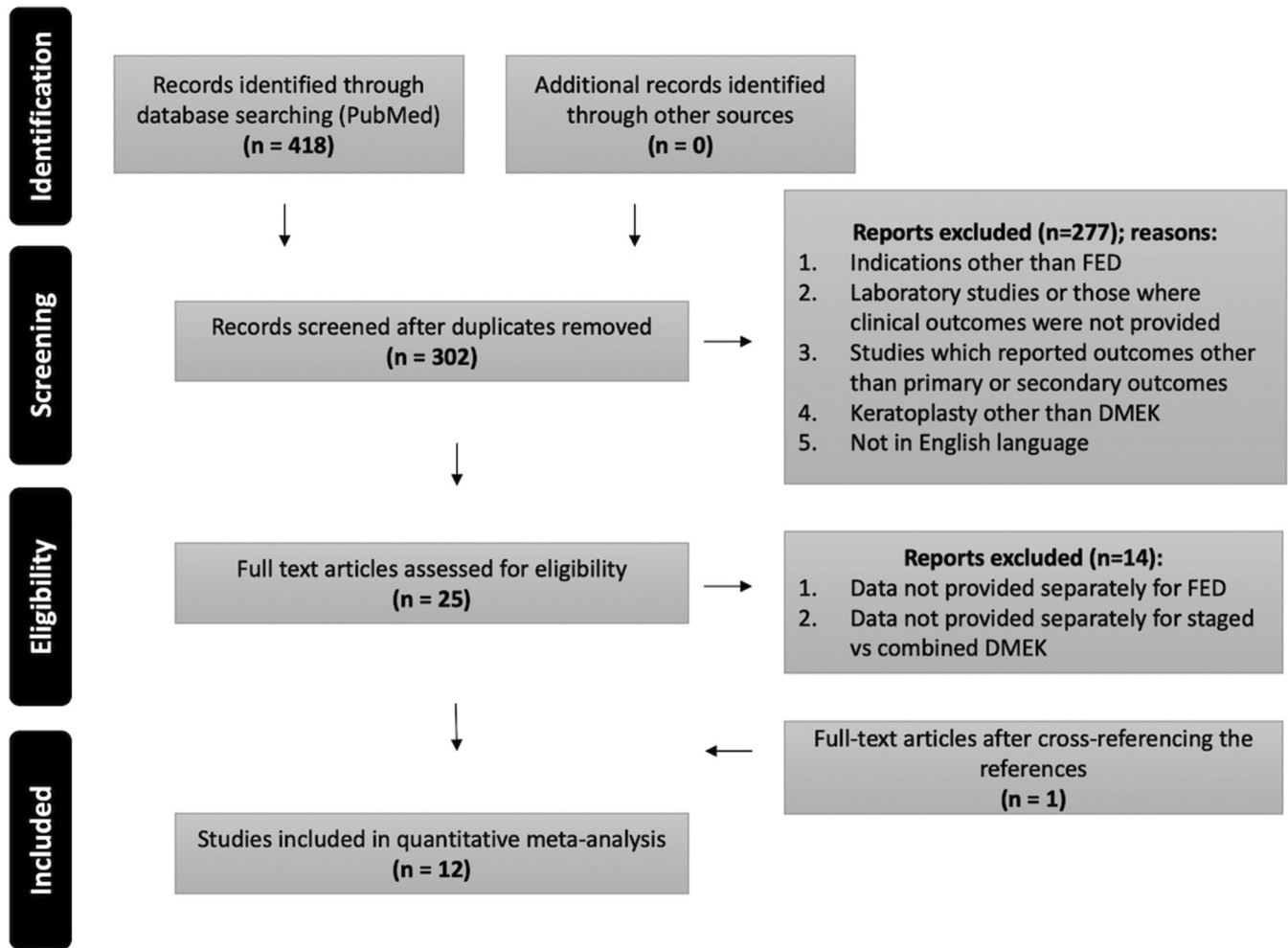


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart

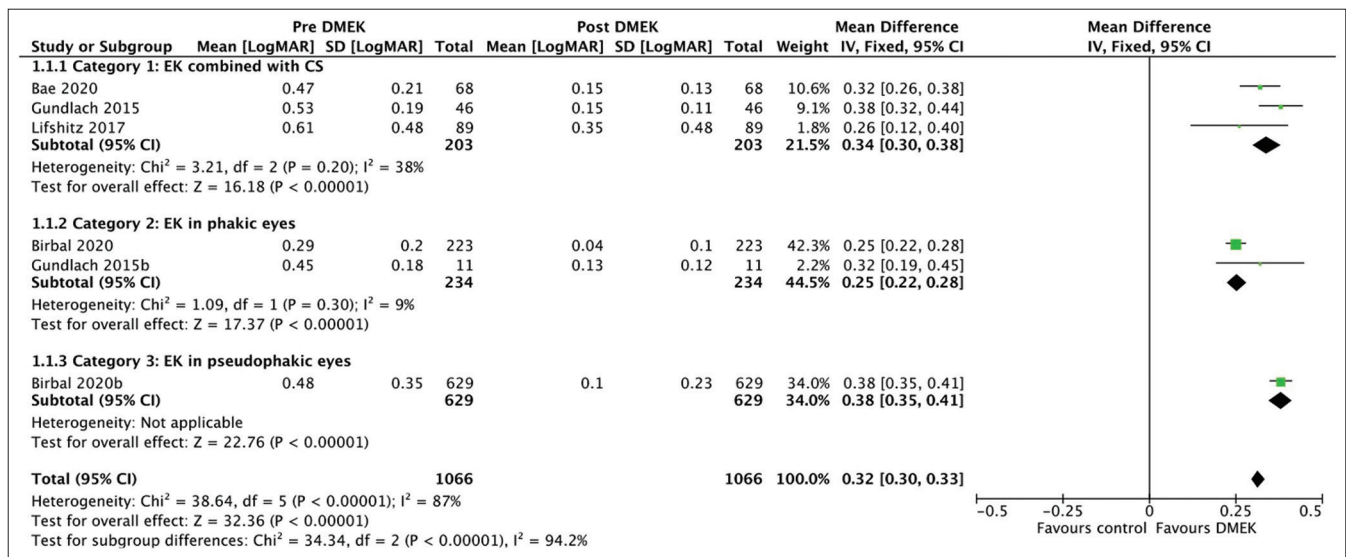


Figure 2: Forest plot showing change in BCVA logMAR at 6 months according to category. At 6 months, there was a mean gain in logMAR BCVA of 0.34 (95% CI 0.30 to 0.38) in category 1, 0.25 (95% CI 0.22 to 0.28) in category 2, and 0.38 (95% CI 0.33 to 0.41) in category 3. Subgroup analysis showed significant difference between categories 1 and 2 and between categories 2 and 3, but no significant difference between categories 1 and 3. BCVA = best-corrected visual acuity, CI = confidence interval, logMAR = log of minimum angle of resolution

P=0.14). At 12 months, there was a mean gain in logMAR BCVA of 0.42 (95% CI 0.25 to 0.60) in category 1 and 0.38 (95% CI 0.32

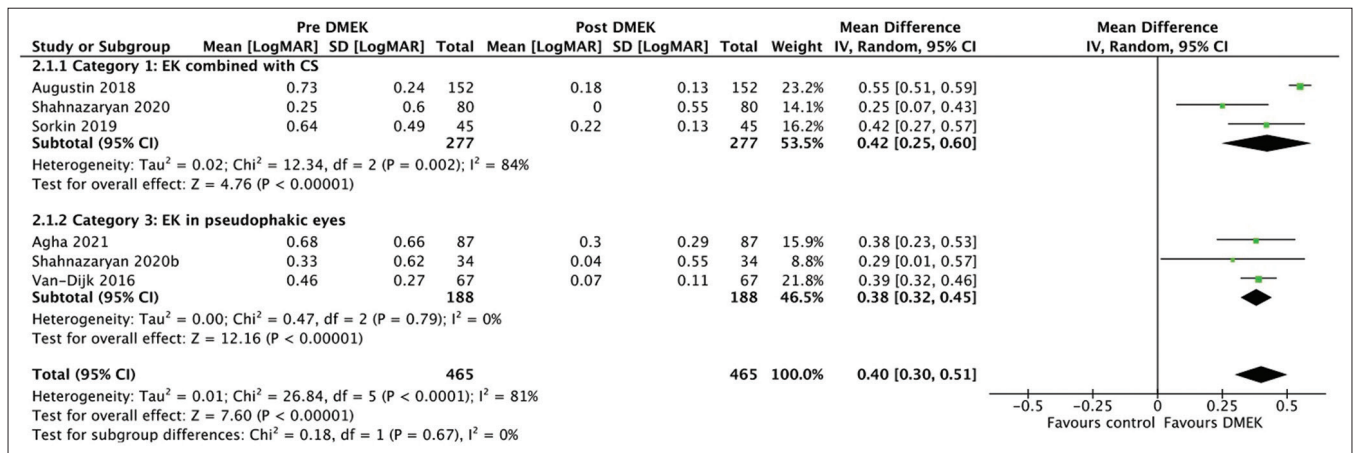
to 0.45) in category 3 (Chi<sup>2</sup> = 0.18, P = 0.67; Fig. 3). There was significant heterogeneity among category 1 studies. No studies



**Table 1: Characteristics of the included studies**

Category	Year	Title of Study	Design*	Eyes
3	2021	Refractive outcome & tomographic changes after DMEK in pseudophakic eyes with FED	RCS	87
1 & 3	2021	Clinical Outcomes of DMEK in Pseudophakic Eyes Compared With Triple-DMEK at 1-Year Follow-up	RCS	108 + 133
1	2020	Refractive Outcomes of DMEK Combined With Cataract Surgery in FED	RCS	68
1 & 3	2020	Endothelial Cell Loss After DMEK for FED: DMEK Compared to Triple DMEK	RCS	80 + 34
1 & 2	2015	DMEK in phakic eyes: targeted therapy or highway to cataract surgery?	RCS	46 + 11
2	2012	Outcomes of DMEK in phakic eyes.	RCCS	52
3	2016	Two-Year Refractive Outcomes After DMEK	PCS	67
1	2019	Three-Year Outcome Comparison Between Femtosecond Laser-Assisted and Manual DMEK	RCS	45
1	2018	Can we predict the refractive outcome after triple DMEK?	RCS	152
1	2017	Comparison of Femtosecond Laser-Enabled Descemetorhexis and Manual Descemetorhexis in DMEK	RCS	89
1	2015	Refractive outcomes of DMEK triple procedures (combined with cataract surgery).	RCS	108
2 & 3	2020	Effect of Surgical Indication and Preoperative Lens Status on DMEK Outcomes	RCS	223 + 629
Studies - 12		Total		Eyes - 1932

DMEK = Descemet's membrane endothelial keratoplasty, FED = Fuchs' endothelial dystrophy, PCS = prospective case series, RCCS = retrospective case-control study, RCS = retrospective case series



**Figure 3:** Forest plot showing change in BCVA logMAR at 12 months according to procedure category. At 12 months, there was a mean gain in logMAR BCVA of 0.42 (95% CI 0.25 to 0.60) in category 1 and 0.38 (95% CI 0.32 to 0.45) in category 3 (Chi<sup>2</sup> = 0.18, P = 0.67). There was significant heterogeneity among category 1 studies. BCVA = best-corrected visual acuity, CI = confidence interval, logMAR = log of minimum angle of resolution

were reporting BCVA at 12 months in category 2, therefore they could not be included in the subgroup analysis.

**Secondary outcomes**

**1. Rebubbling and graft detachment**

Four studies did not provide rebubbling rates;<sup>[18-21]</sup> remaining eight studies were category 1 (n = 3), category 2 (n = 1), category 3 (n = 1), categories 1 & 3 (n = 2), and categories 2 & 3 (n = 1). Rebubbling rate was 15% (95% CI 11 to 18, n = 430) for eyes in category 1, 4% (95% CI 2 to 7, n = 275) in category 2, and 10% (95% CI 8 to 13, n = 883) in category 3, the difference being statistically significant (P < 0.01) [Fig. 4]. Interestingly, Parker *et al.*<sup>[15]</sup> reported zero rebubbling rates in their study of 52 phakic eyes undergoing DMEK alone. Birbal *et al.*<sup>[13]</sup> included both phakic (n = 223) and

pseudophakic eyes (n = 629) and reported a comparable rate for phakic versus pseudophakic FED eyes (5.8% vs. 8.0%, P = 0.56)

Shahnazaryan *et al.*<sup>[17]</sup> compared the outcomes between pseudophakic DMEK (n = 34) and DMEK triple (n = 80) and reported the lowest rate of rebubbling in literature (2.9% and 2.5%, respectively), the difference being statistically insignificant. On the other hand, Fajardo-Sanchez and de Benito-Llopis<sup>[14]</sup> reported rebubbling rates of 25.5% in the pseudophakic DMEK category (n = 133) and 17.6% in the triple-DMEK category (n = 108) (P = 0.13) in their study, with the highest reported rebubbling rate being 33.3% in a study reporting the outcomes of DMEK triple (n = 45). Graft detachment rates were available in two category 1

studies and one each in category 2, category 3, categories 1 & 2, and categories 2 & 3 studies.<sup>[13,15,20-23]</sup> Overall rates were 31% (95% CI 24 to 38,  $n = 180$ ) in category 1, 8% (95% CI 5 to 12,  $n = 286$ ) in category 2, and 13% (95% CI 11 to 16,  $n = 696$ ) in pseudophakic DMEK category ( $n = 696$ ),

the difference between categories being statistically significant ( $P < 0.01$ ) [Fig. 5].

In line with the rebubbling rates, Birbal *et al.*<sup>[13]</sup> reported comparable detachment rates in phakic (9.8%,  $n = 223$ ) and pseudophakic eyes (13.2%,  $n = 629$ ). Gundlach *et al.*<sup>[20]</sup>

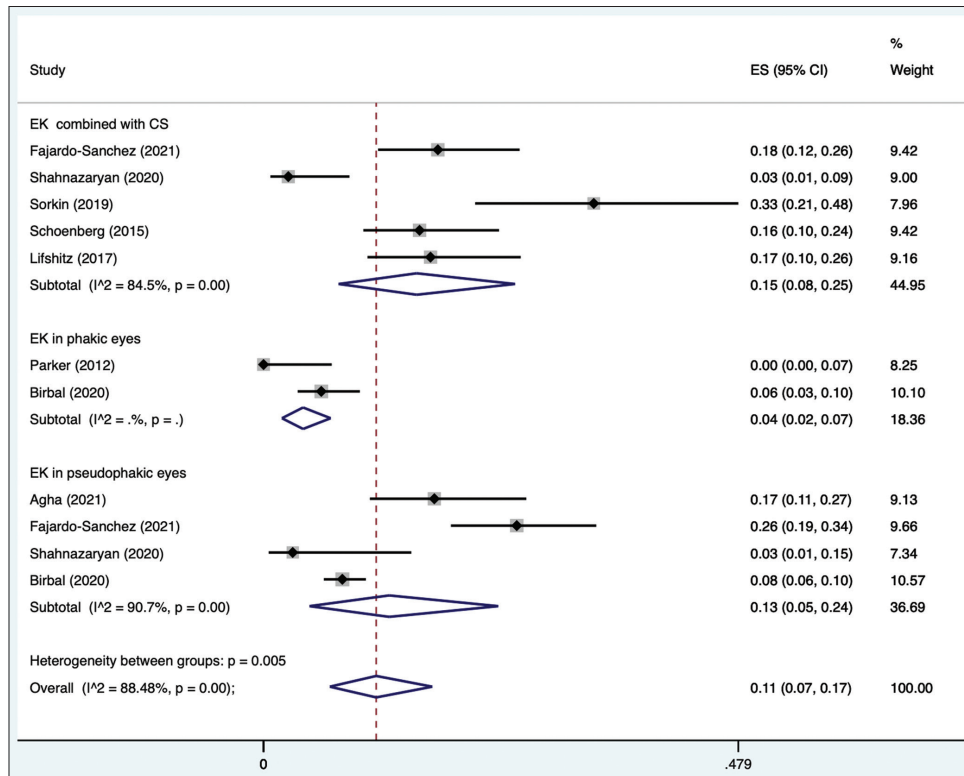


Figure 4: Forest plot showing rebubbling rate at the final follow-up according to procedure category

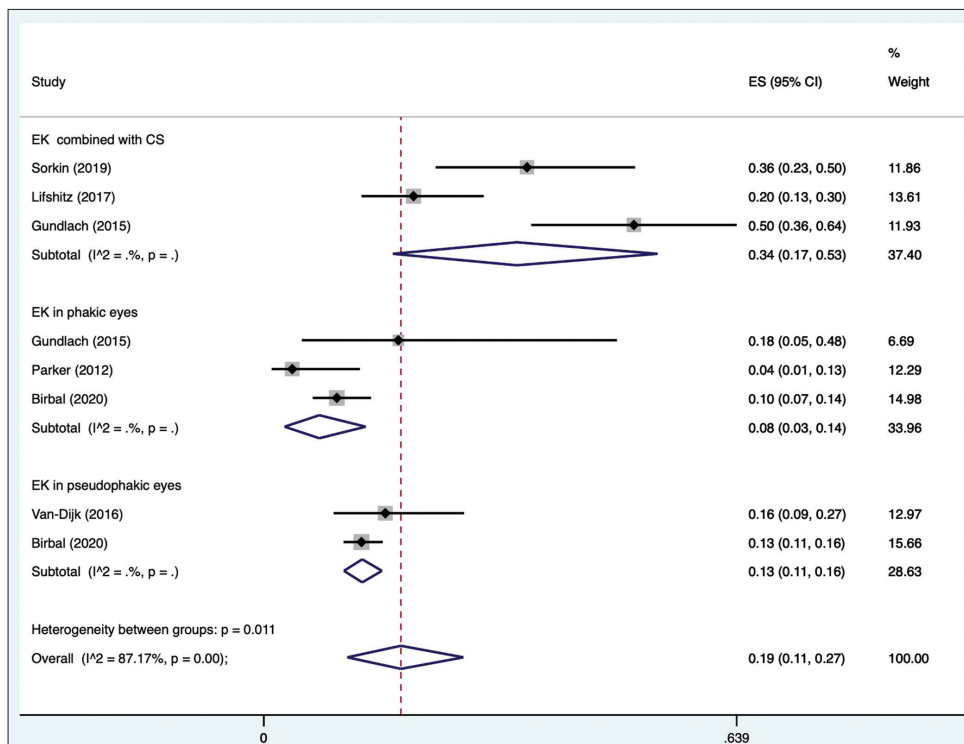


Figure 5: Forest plot showing graft detachment rate at the final follow-up according to procedure category

compared DMEK alone versus in combination with cataract surgery in phakic eyes with FED and found detachment rates of 18% in the phakic DMEK category ( $n = 11$ ) and 50% in DMEK ( $n = 46$ ). However, they did not report their rebubbling rates; the authors noted significantly higher values in the triple category than in the phakic category ( $P = 0.024$ ).

Two studies<sup>[14,22]</sup> reported graft dislocation rates. This was 4.4% in a study of 45 eyes that underwent DMEK triple,<sup>[22]</sup> with graft detachment and rebubbling rates of 35.6% and 33.3%, respectively. The other study<sup>[14]</sup> only provided dislocation rates: 1.8% in the triple DMEK category ( $n = 108$ ) and 2.3% in the pseudophakic DMEK category ( $n = 133$ ); however, this was not statistically significant ( $P = 0.76$ ). Not all studies reporting graft detachment rates reported rebubbling rates and vice versa; however, when both figures were documented, rebubbling rates were consistently lower than detachment rates.

## 2. Refractive SE and astigmatism

Two category 3 studies, one category 2 study, and one study with both category 1 and 2 eyes reported refractive outcomes, viz., preoperative and postoperative SE and refractive cylinder; however, in the latter study, refractive targets were adjusted by  $-0.5$  D to account for expected hyperopic shift.<sup>[15,20,21,24]</sup> Further, two category 1 studies only reported the post-op SE. Due to this reason and limited data, reporting an average change in different categories was not feasible.

In category 1, a statically significant hyperopic shift was noted in all three studies. Bae *et al.*<sup>[19]</sup> adjusted the refractive targets myopically by approximately  $0.50$  D in their study of 68 eyes undergoing DMEK triple. They found that the mean SEs at six months were  $-0.14 \pm 1.26$ D, representing a

mean hyperopic shift of  $0.55$  D from the target. Augustin *et al.*<sup>[18]</sup> found a mean refractive shift of  $1.12 \pm 110$  D at 3 months from surgery ( $n = 152$ ), which remained stable until the last follow-up at 12 months ( $1.24 \pm 1$  D). Further, the authors noted a weak but significant positive correlation between refractive shift and preoperative posterior curvature ( $\rho = 0.314$ ,  $P = 0.02$ ) or preoperative posterior densitometry ( $\rho = 0.227$ ,  $P = 0.008$ ).

In category 2, Parker *et al.*<sup>[15]</sup> noted a change in SE from  $-0.76 \pm 2.2$  D preoperatively to  $0.01 \pm 2.1$  D at 3 months and  $-0.02 \pm 2.1$  D at 6 months after DMEK ( $n = 43$ ). The preoperative to postoperative change in SE (hyperopic and myopic shifts in corneal power averaged) was statistically significant at 3 and 6 months (both  $P < 0.01$ ). Gundlach *et al.*<sup>[20]</sup> reported refractive outcomes in both category 1 and 2 eyes. They reported mean refractive SE of  $0.19 \pm 3.14$  D preoperatively and  $-0.20 \pm 1.14$  D after 6 months ( $P = 0.46$ ) in category 1 and  $-0.75 \pm 3.53$  D preoperatively and  $-0.63 \pm 3.53$  D after 6 months ( $P = 0.26$ ) in category 2. Though there was no statistically significant difference in either category, it is essential to note that the refractive target was adjusted by  $-0.5$  D in category 1 to account for the expected hyperopic shift.

In category 3, there was a trend toward a hyperopic shift in the mean refractive SE after DMEK; however, it was not statistically significant. Agha *et al.*<sup>[24]</sup> reported an increase in mean SE ( $\pm$ SD) from  $+0.04 \pm 1.73$  to  $0.37 \pm 1.30$  D at the final follow-up visit after DMEK. Still, although there was a slight hyperopic shift in all three subcategories of preoperatively emmetropic, myopic, and hyperopic eyes, the total refractive changes were statistically not significant ( $P = 0.06$ ). van Dijk *et al.*<sup>[21]</sup> reported a mean change in SE of  $+0.33$  D (95% CI =  $0.11$  to  $0.54$ ,  $P = 0.03$ ) at 3 months, but this stabilized

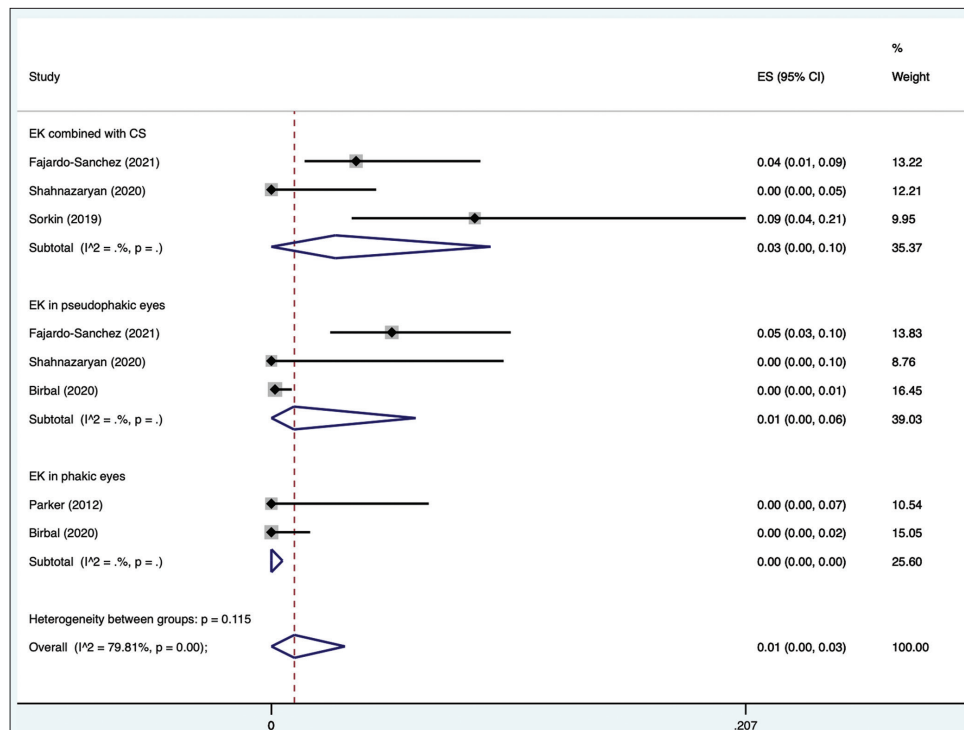


Figure 6: Forest plot showing primary failure rate at the final follow-up according to procedure category



at 6 months ( $P = 0.46$ ) and was maintained up to 2-year follow-up ( $P = 0.92$ ).

None of the studies reporting refractive astigmatism found any significant change after surgery in all categories. Gundlach *et al.*<sup>[20]</sup> did not note any significant change in the refractive cylinder in either category 1 ( $P = 0.78$ ) or 2 eyes ( $P = 0.67$ ). Mean refractive astigmatism was  $1.22 \pm 1.16$  D preoperatively and  $1.00 \pm 1.13$  D at 6 months after surgery in phakic eyes undergoing DMEK ( $n = 11$ ) and  $1.24 \pm 1.23$  D preoperatively and  $1.15 \pm 0.94$  D at 6 months after surgery in phakic eyes undergoing DMEK triple ( $n = 46$ ). In their study of 52 category 2 eyes, Parker *et al.*<sup>[15]</sup> noted no statistically significant change from preoperative to postoperative refractive cylinder (hyperopic and myopic shifts in cylindrical power averaged) at 3 months ( $P = 0.76$ ) or 6 months ( $P = 0.82$ ).

In category 3, Agha *et al.*<sup>[24]</sup> did not note any significant changes in topographic parameters, such as anterior corneal astigmatism and simulated keratometry, though posterior corneal astigmatism decreased from  $0.59 \pm 0.56$  to  $0.39 \pm 0.27$  D ( $P < 0.01$ ). van Dijk *et al.*<sup>[21]</sup> also did not find any significant change in the mean refractive cylinder from before to any evaluated postoperative follow-up ( $P = 0.31$ ); however, they reported significant variations in individual cases.

3. Endothelial cell loss

Five studies did not provide data for endothelial cell loss (ECL); these included two category 1, two category 3, and one study with categories 1 & 3 eyes.<sup>[14,18,19,21,24]</sup> The maximum follow-up was 12 months for categories 1 and 3 (range: 6–12 months), but only 6 months for category 2. The weighted average ECL was calculated at the last follow-up visit; this was  $32.3\% \pm 5.9\%$  for category 1,  $38.2\% \pm 2.0\%$  for category 2, and  $38.7\% \pm 1.9\%$  for Category 3.

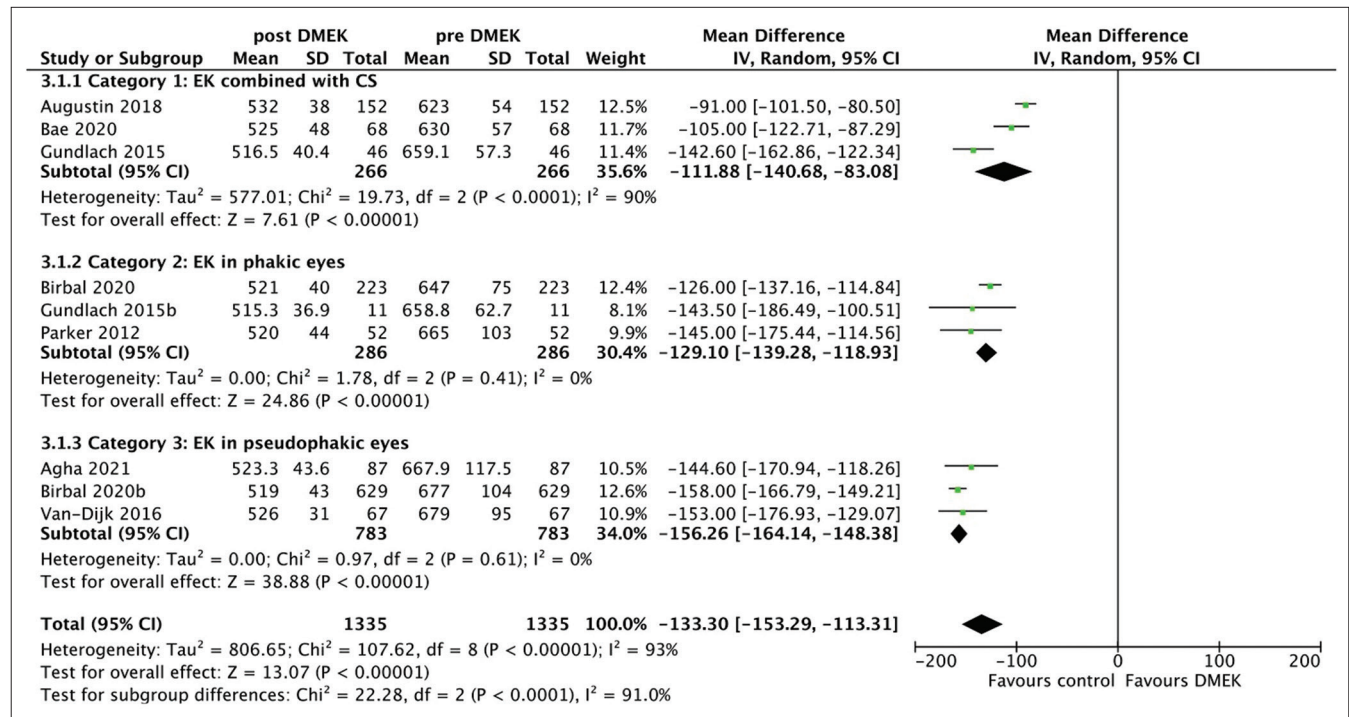
Shahnazaryan *et al.*<sup>[17]</sup> compared category 1 and category 3 eyes and found significantly less ECL in pseudophakic DMEK than in the triple-DMEK category at both 1 month (95% CI 1.67 to 15.02,  $P = 0.02$ ) and 1 year (95% CI 1.06 to 14.07;  $t$ -test,  $P = 0.03$ ) after surgery. In their study, the mean preoperative donor ECDs were  $2630 \pm 194$  and  $2643 \pm 197$  cells/cm<sup>2</sup> in category 3 and category 1 eyes, respectively. At 1 month, the mean ECDs were  $1968 \pm 476$  and  $1737 \pm 422$  cells/cm<sup>2</sup> in DMEK-only and triple-DMEK categories, respectively, representing ECL of 25% and 35%, respectively, from preoperative donor ECDs. At 1 year, the mean ECDs were  $1748 \pm 427$  and  $1511 \pm 437$  cells/cm<sup>2</sup> in DMEK-only and triple-DMEK categories, respectively, representing ECL of 33% and 41%, respectively.

Gundlach *et al.*<sup>[20]</sup> compared category 1 and 2 eyes and noted a steady decline in endothelial cell density in both categories. In category 1, the mean endothelial cell count was  $2290.0 \pm 174.8$  mm<sup>2</sup> preoperatively and  $1676.8 \pm 355.2$  mm<sup>2</sup> at 6 months postoperatively ( $P = 0.008$ ), corresponding to a medium loss of 27%. In category 2, the mean endothelial cell count was  $2330.1 \pm 180.5$  mm<sup>2</sup> preoperatively and  $1529.7 \pm 695.6$  mm<sup>2</sup> at 6 months postoperatively ( $P = 0.01$ ), corresponding to a medium loss of 34%. However, they did not compare the ECL in the two categories.

Birbal *et al.*<sup>[13]</sup> compared category 2 and 3 eyes and noted an average ECL of  $39\% \pm 17\%$  in the phakic DMEK category ( $n = 203$ ) and  $39\% \pm 18\%$  in the pseudophakic DMEK category ( $n = 582$ ) at 6 months, the difference being statistically insignificant ( $P = 0.85$ ).

4. Graft rejection

There was limited data available for analysis for graft rejection. Therefore, only the individual reported values are discussed.



**Figure 7:** Forest plot showing change in CCT at the final follow up according to procedure category. The mean change in CCT (µm) (95% CI) was statistically significant ( $P < 0.01$ ) between the categories:  $-112$  ( $-141$  to  $-83$ ) in category 1,  $-129$  ( $-139$  to  $-119$ ) in category 2, and  $-156$  ( $-164$  to  $-148$ ) in category 3. CCT = central corneal thickness, CI = confidence interval

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Sorkin *et al.*<sup>[22]</sup> noted one graft rejection during the 12 months follow-up in their study of 45 category 1 eyes, which resolved ultimately with topical steroidal treatment. Einar-Lifshitz *et al.*<sup>[23]</sup> noted zero cases of graft rejection in their study of 89 category 1 eyes within 6 months, and so did Parker *et al.*<sup>[15]</sup> in their study of 52 category 2 eyes. Birbal *et al.*<sup>[13]</sup> noted 0% for category 2 ( $n = 223$ ) and 0.6% for category 3 ( $n = 629$ ) eyes within 6 months after surgery (no  $P$  value). All cases were successfully managed by applying an intensified regimen of topical corticosteroids.

Two studies compared category 1 and 3 eyes and noted similar graft rejection rates in the two categories, though the rates varied between the two studies.<sup>[14,17]</sup> While Fajardo-Sanchez and de Benito-Llopis<sup>[14]</sup> reported graft rejection rates of only 1% and 3.2% in category 1 ( $n = 111$ ) and category 3 ( $n = 218$ ) eyes, respectively, at 1 year ( $P = 0.19$ ), Shahnazaryan *et al.*<sup>[17]</sup> reported graft rejection rates of 8.75% and 8.8% in category 1 ( $n = 80$ ) and category 3 ( $n = 34$ ) eyes, respectively, at 1 year ( $P = 0.50$ ). However, the authors of the latter study reported 0% graft failure in 1 year, indicating that all rejection cases were successfully managed.

#### 5. Graft failure

Various studies reported either or both of primary graft failure (a graft which fails to clear) and late endothelial failure; the latter, also commonly known as endothelial graft failure, is defined as a graft that cleared in the initial postoperative period, generally in the first 8 weeks, but subsequently became cloudy because of presumed endothelial cell attrition. There was no difference in the primary failure among the three categories ( $P = 0.12$ ); it was 3% (95% CI 0 to 10,  $n = 233$ ) in category 1, 0% (95% CI 0 to 0,  $n = 275$ ) in category 2, and 1% (95% CI 0 to 6,  $n = 796$ ) in category 3 [Fig. 6].

Sorkin *et al.*<sup>[22]</sup> reported four primary graft failures (8.9%) in their study of 45 category 1 eyes: two were secondary to complete detachment and two followed partial detachment and rebubbling. No endothelial failures were observed throughout the 12 months follow-up.

Fajardo-Sanchez and de Benito-Llopis<sup>[14]</sup> reported primary failure and endothelial failure rates within 12 months of 3.7% and 2.8%, respectively, in category 1 eyes ( $n = 108$ ) and 5.2% and 2.3%, respectively, in category 3 eyes ( $n = 133$ ); the rates were comparable for both types between the two

categories ( $P > 0.05$ ). Interestingly, Shahnazaryan *et al.*<sup>[17]</sup> noted zero cases of both primary failure and endothelial failure of category 1 ( $n = 80$ ) and category 3 ( $n = 34$ ) eyes within 1 year in their study.

Parker *et al.*<sup>[15]</sup> also did not report any case of primary or endothelial failure in 52 category 2 eyes within 6 months of follow-up. Similarly, Birbal *et al.*<sup>[13]</sup> who compared phakic and pseudophakic DMEK, did not find any case in category 2, but reported 0.2% primary failure with 0% endothelial failure at 6 months in category 3.

#### 6. Central corneal thickness

Four studies did not provide CCT data; these included three category 1 studies and one study including categories 1 & 3.<sup>[14,16,17,22]</sup> Preoperative weighted mean CCT was  $620.7 \pm 24.4$ ,  $650.7 \pm 8.7$ , and  $676.1 \pm 3.6$   $\mu\text{m}$  in categories 1, 2, and 3, respectively ( $P = 0.033$ ); this improved to  $528.1 \pm 2.4$ ,  $520.6 \pm 1.3$ , and  $519.9 \pm 2.6$   $\mu\text{m}$ , respectively, at the latest postoperative visit ( $P = 0.23$ ). The mean change in CCT ( $\mu\text{m}$ ) (95% CI) was statistically significant ( $P < 0.01$ ) among the categories:  $-112$  ( $-141$  to  $-83$ ) in category 1,  $-129$  ( $-139$  to  $-119$ ) in category 2, and  $-156$  ( $-164$  to  $-148$ ) in category 3 [Fig. 7].

#### 7) Other complications

No serious complications were reported by any studies included in our literature review.

##### a. Cataract surgery after phakic DMEK

Birbal *et al.*<sup>[13]</sup> reported that 0.9% (two out of 223) of phakic DMEK eyes in category 2 required cataract surgery within 6 months of transplant. Gundlach *et al.*<sup>[20]</sup> reported cataract surgery in two patients at 12 months after phakic DMEK ( $n = 11$ ); they further reported uneventful surgery and stable endothelial cell density 6 weeks after surgery.

Parker *et al.*<sup>[15]</sup> mentioned the need for phacoemulsification in two eyes out of the total 52 eyes (4%) at 6 months and 2.5 years after the initial DMEK surgery, respectively. Both eyes were noted to have anterior subcapsular opacifications within the first month after DMEK. The authors attributed this to air-bubble misdirection in the immediate postoperative phase behind the iris. After surgery, they further noted five other eyes (10%) developing faint anterior capsular haze (like glaucoma flecks). Still, all had similar visual acuity at 6 months of follow-up compared to the overall category of phakic eyes.

##### b. Glaucoma

In the study by Gundlach *et al.*<sup>[20]</sup> in the first 6 months, two patients from the phakic category demonstrated elevated intraocular pressure (IOP): one was a steroid responder and the other was known to have glaucoma. Both patients demonstrated normal pressure after a change in local steroid therapy or intensifying local glaucoma therapy. In the triple-procedure category, four patients displayed increased pressure: one patient exhibited a steroid response, two had previous glaucoma, and one developed secondary glaucoma. In the study by Parker *et al.*<sup>[15]</sup> mechanical angle-closure glaucoma caused by air-bubble misdirection behind the iris in the immediate postoperative phase was observed in six eyes (11.5%). Authors noted a tendency for air to move under the iris intraoperatively in all these eyes. In one patient with preexisting open-angle glaucoma,

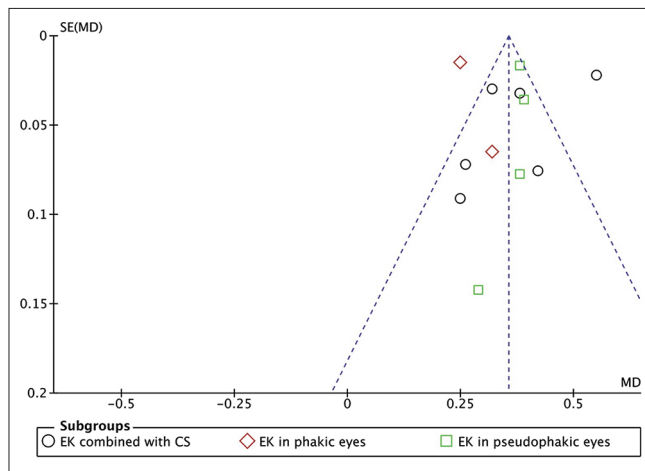


Figure 8: Funnel plot of the included studies for the primary outcome



they reported intermittent glaucomatous crises within the first 6 months after surgery, necessitating secondary glaucoma surgery for control of IOP.

In the study by Sorokin *et al.*,<sup>[22]</sup> two eyes in the M-DMEK (manual DMEK) category had IOP elevation during follow-up, which was attributed to steroid response. IOP normalized in the first eye following a change of the topical steroid and in the second eye following initiation of one topical IOP-lowering medication.

Birbal *et al.*<sup>[13]</sup> reported retransplantation rates within 6 months after phakic and pseudophakic DMEK; these did not differ between the two categories ( $P > 0.05$  for all comparisons). In category 2 ( $n = 223$ ), four eyes required re-DMEK (1.8%) and none of the eyes needed secondary Descemet's stripping endothelial keratoplasty (DSEK) or penetrating keratoplasty (PK). In category 3 ( $n = 629$ ), four eyes required re-DMEK (0.6%) and six eyes required secondary DSEK; none of the eyes needed secondary PK.

### Assessment of bias

A symmetrical funnel plot indicated publication bias was unlikely for the studies included in the primary outcome [Fig. 8].

## Discussion

DMEK has become an increasingly popular procedure for endothelial dysfunction due to its advantages over total thickness corneal grafts and DSEK in visual rehabilitation, operative time, and reduced rates of graft rejection and failure.<sup>[1]</sup> The most common indication for performing DMEK is FED, wherein many patients may also need concurrent management for cataracts.<sup>[5,25]</sup> This is a review that summarizes the published evidence of outcomes and complications of DMEK performed with, before, or after cataract surgery.

We review and analyze the reported outcomes for 1932 eyes from 12 studies that underwent DMEK. As expected, the mean age of patients who underwent phakic DMEK was significantly lower, with the highest age category being for patients who underwent pseudophakic DMEK. This is often seen in clinical practice, as younger patients are less likely to have visually significant cataracts. Similarly, the preoperative CCT was highest in the pseudophakic DMEK category and lowest in the phakic DMEK category; the statistically significant trend was maintained in the mean change in CCT with comparable final postoperative CCT in all three categories.

Baseline best-corrected distance visual acuity was comparable in all three categories; however, mean gain in BCVA at 6 months was significantly lower for phakic DMEK compared to the other two categories. This could be influenced by the development of visually significant cataract, with rates reported from 1% to 14% within 1 year among the included studies. BCVA was comparable in DMEK triple and pseudophakic DMEK at 6 and 12 months, respectively. Shahnazaryan *et al.*,<sup>[17]</sup> in their retrospective case series, reported excellent and comparable visual acuity outcomes in DMEK triple and pseudophakic DMEK. In another retrospective design study by Birbal *et al.*,<sup>[13]</sup> visual acuity outcomes were found to be similar between phakic and pseudophakic FED eyes, when corrected for age and preoperative BCVA.

A common argument for performing pseudophakic DMEK, viz., triple DMEK, is that many surgeons find that a section of patients may gain reasonably good visual acuity after cataract surgery and may not require further corneal transplant. Though this decision, if often based on patient-related factors, such as age, ease of attending regular follow-ups, timing between previous cataract surgery and subsequent DMEK, might help in guiding this decision. Only one study (category 3) included in the meta-analysis recorded the median time interval between previous cataract surgery and DMEK and this was 12 months (range: 2–112 months).<sup>[24]</sup>

Analysis of refractive outcomes revealed hyperopic shift after all DMEK surgeries, which was statistically significant for individually reported results in all category 1 and 2 studies, though not achieving statistical significance for the entire category. For phakic eyes, Gundlach *et al.*<sup>[20]</sup> reported no difference in the refractive outcomes for DMEK performed with or without cataract surgery. There was no significant change in refractive astigmatism reported for any of the categories.

Graft detachment and rebubbling rates were highly variable between studies; however, the cumulative analysis indicated the highest rates for both in DMEK triple compared to the other two categories. ECL ranged from 27% to 41% at the last follow-up visit across all eyes; however, statistical analysis was not possible. Weighted average ECL was lower in triple DMEK compared to pseudophakic DMEK, though the rates were comparable between the latter and phakic DMEK. Consequently, there was no significant difference in graft failure and graft rejection rates, which were comparable among the three categories as reported in individual studies.

A recent study by Moshiri *et al.*<sup>[26]</sup> comparing the three categories in a retrospective cohort study, which was not published at the time of literature review, reported that phakic and triple DMEK procedures tend to have a better 1-year Best spectacle corrected visual acuity (BSCVA) than pseudophakic DMEK, with no differences in other parameters analyzed, viz., CCT, graft detachment, and rebubbling rates. However, they did not analyze the mean gain in BSCVA and discussed that patients from pseudophakic DMEK group were older and already had worse BSCVA before surgery. In another recent retrospective comparative case series,<sup>[8]</sup> not included in the analysis, which compared the outcomes of triple DMEK versus pseudophakic DMEK in patients with FED, the authors found no significant difference in visual outcomes, ECL, and rebubbling rates between the two groups.

The main limitation of this review is a lack of prospective studies and clinical trials, as most studies were retrospective in design. Further results should be interpreted with caution due to the high risk of study design bias and unequal distribution of the number of eyes in each category and for different outcomes. However, our results have important implications for future research. We have highlighted the need for high-quality studies in combined and staged DMEK. There was an apparent inconsistency between the retrospective studies in reporting significant efficacy and safety outcomes. We recommend that all future studies report findings of the headings used to assess the safety and efficacy in this review to aid standardization.

## Conclusion

In summary, the mean gain in BCVA in DMEK triple was comparable to category pseudophakic DMEK at 6 and 12 months. Although rebubbling and graft detachment rates were highest in DMEK triple compared to other categories, there was no clinically meaningful difference in overall graft rejection, graft survival rates, and ECL.

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## Conflicts of interest

There are no conflicts of interest.

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