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Femtolaser-assisted keratoplasty: Surgical outcomes and benefits

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ABSTRACT

Femtosecond laser technology has evolved as an alternative method to make surgical incisions in keratoplasty. The use of this approach has a number of purported advantages that may lead to superior clinical outcomes. However, there remains a low uptake of the femtolaser-assisted keratoplasty within public healthcare, and incongruity remains between perceived expert opinion on the presence and significance of superior clinical outcomes based on available data.

This review is registered publicly on the Open Science Framework registry and aims to evaluate the evidence base on femtolaser-assisted keratoplasty and its comparison with manual trephination in intraoperative and postoperative outcomes. Over 2000 studies were screened and critically appraised in the field of keratoplasty, using multiple databases. 17 studies were included via predetermined criteria for full analysis. The studies covered interventional research into penetrating keratoplasty (PK), deep anterior lamellar keratoplasty (DALK), and posterior lamellar keratoplasty (PLK).

The results of this review show that PK studies shared a trend of improved visual outcomes with the femtolaser, and evidence for earlier suture removal. Complication rates were similar. When used for DALK, studies showed some evidence of improved visual outcomes with the femtolaser, and evidence for earlier suture removal, reduced intraoperative complications and increased wound healing activity. The use in Descemet's membrane endothelial keratoplasty (DMEK) showed reduced graft detachment whereas in Descemet's stripping automated endothelial keratoplasty (DSAEK) the results were limited.

Overall, this review shows a trend that the use of the femtolaser may improve clinical outcomes in PK, DALK and DMEK. However, it was also clear that in order to corroborate the superiority of femtolaser-assisted keratoplasty versus manual methods, further research is required.

1. Introduction

The first use of the infrared femtosecond laser (femtolaser/FS-laser) to make incisions in corneal transplant keratoplasty was documented in 2000 [1]. Since, then there has been substantial progression in application of this technology to keratoplasty surgery, with improvement in the depth of laser delivery, dedicated corneal applanation hardware and laser surgical platforms that have integrated anterior segment imaging technologies [2].

Since inception, there has been a long-held belief that the higher surgical precision of femtolaser-assisted keratoplasty would lead to superior outcomes, when used over manual methods. Additionally, the femtolaser's associated guidance systems provides novel capabilities such as improved surgical centration and profiled incisions. The femtolaser can produce surgical graft profiles such as 'top-hat', 'mushroom' and 'zig-zag' shapes, which are difficult to achieve using conventional/manual surgical trephines [3]. These wound constructions offer theoretical advantages of an increased wound surface area, lower surgically associated astigmatism and less non-astigmatic aberrations.

Furthermore, the use of laser approaches may improve and strengthen wound healing, while the increased surface area of some profiles may also improve biomechanical stability [4].

These properties have the potential for fewer sutures or even sutureless surgery [5]. Finally, the inherent automatability and repeatability of the femtolaser may lessen the steep learning curve of lamellar corneal transplant surgery [6], and decrease complications.

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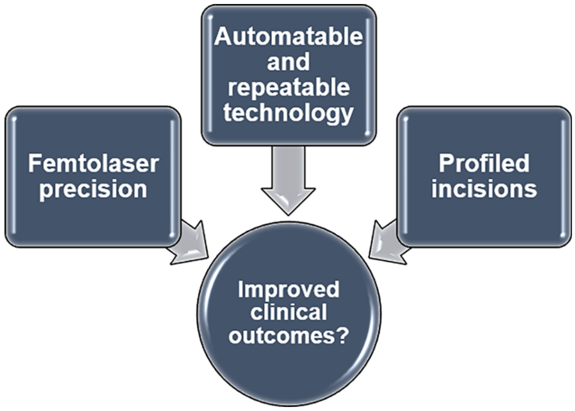

Fig. 1. The advantageous properties of the femtolaser suggest improved clinical outcomes may be seen in its use over manual methods.

The aforementioned surgical features and theoretical advantages should result in improved clinical outcomes when compared with manual methods (Fig. 1) [7,8], and the application of femtolaser technology to keratoplasty is predicted to hold an important role in the future. With this rationale in mind, there have been several clinical studies that investigate femtolaser-assisted keratoplasty [8,9]. A significant proportion of this research has been observational studies. These are valuable in confirming efficacy, safety and reliability [10–12], but are limited in substantiating the potential advantages of the femtolaser compared with manual methods.

20 years after the femtolaser's first use in keratoplasty, there is an apparent incongruity in both expert opinion and evidence on any superiority of femtolaser-assisted keratoplasty to manual methods [13,14], and current uptake into public healthcare systems remains low [15].

1.1. Rationale and objectives

In this review we will review and assess the evidence base of interventional studies investigating femtolaser-assisted keratoplasty as compared to manual methods. Dissemination of these studies may aid in substantiating advantages in outcomes the femtolaser may have and give insight for researchers/clinical decision makers in understanding what is known about femtolaser-assisted keratoplasty and future directions of the surgical technology.

2. Methods

2.1. Registration

This review is registered publicly on the Open Science Framework registry, DOI: https://doi.org/10.17605/osf.io/adnr2. This review received local ethical approval and sponsorship through the University of Southampton Ethics and Research Governance Online (ERGO) system [ERGO reference no. 26607.A1].

2.2. Eligibility criteria

Inclusion criteria was as follows:

Population: Adults undergoing keratoplasty, for any indication.
Intervention: Femtolaser-assisted keratoplasty must be applied to at least one group in the study.
Comparison: Same keratoplasty procedure as done by manual methods.
Outcomes: Intra and postoperative clinical outcomes.
Design: Randomised and non-randomised, interventional studies to be included.

There were no date or language constraints, although studies were liable for exclusion later should no suitable translation be acquired.

2.3. Search strategy

The search strategy is outlined in appendix B. Searches used text words over Medical Subject Headings (MeSH) terms as this review focuses on a very subspecialized subject. Unique search terms may be better used with text word search than MeSH [16]. Where conjugated searches were not possible (e.g. Europe PMC) an alternative search was used, made as close to the main search strategy as possible.

2.4. Study selection and information sources

Appendix A shows the study selection and data sources for this review. Two searches were carried out using the same search strategy. The first was completed in December 2017, and the second in April 2019. PICOD criteria for study inclusion was different in the two search processes. The PICOD criteria used in 2019 was an adapted version of the 2017 criteria (2017 PICOD criteria is in Appendix C), and so this criteria was applied retrospectively to the searches done in 2017.

2.5. Data collection process

For full text screening, papers' full text pdfs were managed on Clarivate Analytics' EndNote. Once included for analysis, bespoke Microsoft Word tables were used for data extraction.

2.6. Risk of bias

Joanna Briggs Institute (JBI) systematic review tools were used for appraisal [17].

2.7. Summary measures

The principal summary measures in included studies were differences in mean, except for Shehadeh-Mashor and Pilger et al. who measured median values.

3. Results

The selection process outlined in appendix Figs. A.1 and A.2 left 17 studies for qualitative synthesis. All papers did their statistical tests at 95% confidence levels. For dissemination, the studies are subdivided into homogenous groups by keratoplasty depth investigated in Sections 4, 5 and 6.

4. Femto-PK vs. manual-PK

Studies were found comparing manual techniques to femtolaser-assisted penetrating keratoplasty. Study characteristics are shown in Table 1.

4.1. Femto-PK indications

Gaster RN and Levinger et al. only investigated patients with keratoconus. The remaining five studies included patients with a variety of ocular conditions requiring PK, e.g. keratoconus, Fuch's dystrophy and bullous keratopathy, amongst others.

4.2. Femto-PK visual acuity

Visual Acuity results are shown in Table 2.

Farid et al. also presented that significantly more femto-PK eyes reached a visual acuity ≥ 20/40 at 1 and 3 months.

Daniel et al. further reported that at 24 months, 70% of their femto-

Table 1
Study characteristics of studies comparing femto-PK with manual-PK.

Study name	Author(s) and year published	N in FS-laser group (eyes)	N in control group (eyes)	Location	FS-keratoplasty graft profile
Clinical Outcomes of Penetrating Keratoplasty Performed with the VisuMax Femtosecond Laser System and Comparison with Conventional Penetrating Keratoplasty	Kamiya et al. (2014) [18]	20	20	Japan	Spherical with 90* side cut angle
Comparison of Femtosecond Laser-assisted Keratoplasty versus Conventional Penetrating Keratoplasty	Chamberlain et al. (2011) [19]	50	50	Portland, USA	Zig-zag
Comparison of Long-Term Outcomes of Femtosecond Laser-Assisted Keratoplasty with Conventional Keratoplasty	Daniel et al. (2016) [20]	141	1254	Freiburg, Germany	Mushroom and top-hat
Penetrating keratoplasty using femtosecond laser enabled keratoplasty with zig-zag incisions versus a mechanical trephine in patients with keratoconus	Gaster RN et al. (2012) [21]	66	71	Beverly Hills, USA	Zig-zag
Outcome of "mushroom" pattern femtosecond laser-assisted keratoplasty versus conventional penetrating keratoplasty in patients with keratoconus	Levinger et al. (2014) [22]	33	26	Jerusalem, Israel	Mushroom
Femtosecond laser versus manual dissection for top hat penetrating keratoplasty	Bahar et al. (2009) [23]	23	71	Toronto, Canada	Top-hat
Comparison of Penetrating Keratoplasty Performed with a Femtosecond Laser Zig-Zag Incision versus Conventional Blade Trephination	Farid et al. (2009) [24]	49	17	Irvine, USA	Zig-Zag

PKs reached a visual acuity of 10/20 or better, the legal requirement to drive in Germany, as opposed to 50% of their manual-PK eyes.

4.3. Femto-PK refraction

Kamiya et al. found their femto-PKs was significantly superior than manual in refractive astigmatism at 1 month. This trend was repeated at 3 and 6 month follow-up in refractive and corneal astigmatism. Farid et al. found significantly superior corneal astigmatism in their femto-PKs at 1 and 3 months and presented a trend that showed for patients with high pre-operative (> 5D) astigmatism in femto-PKs, the mean value decreased at each follow-up point. For the same group of manual-PK patients, this trend was absent. Gaster et al. and Chamberlain et al. also found significantly superior topographic astigmatism at 6 months in their FS groups, with Chamberlain et al. finding a further significantly superior result at 20 + months.

Bahar et al. found at 12 months that their femto-PKs had two significantly superior results to each of their two control groups; superior compared to their manual top-hat group (N = 36) in spherical equivalent refraction, and superior compared to the manual, 90° side-cut group (N = 35) in total no. of high order spherical aberrations in the 6 mm optic zone. Levinger et al. found significantly better manifest cylinder refraction and blurring strength at 12 months in their femto-PKs.

Daniel et al. found their manual-PKs at 24 months to be significantly superior to their femto-PKs in spherical equivalent refraction.

4.4. Femto-PK complications

Farid et al. did not report complications. The remaining six studies encountered no intraoperative complications, in manual-PKs or femto-PKs.

Kamiya et al. found that their manual-PKs experienced more postoperative complications (two graft rejections, three raised IOPS and one infection) than their FS-group (one graft rejection).

Bahar et al. Gaster RN et al. Chamberlain et al. and Levinger et al. found a similar number of postoperative complications between their two groups. Complications included graft rejection, failure and raised IOP.

Out of Daniel et al's three groups, their FS-mushrooms (N = 34) experienced the most postoperative complications (17.6% complication rate) and their FS-top-hats (N = 107) the least (5.6%). Their manual-PK's complication rate was 12.6%.

4.5. Other outcomes

Suture removal

Chamberlain et al. noted significantly more sutures were removed at 3 and 6 months for their femto-PKs compared to manuals. Bahar et al. also noted that sutures were removed significantly earlier in their femto-PKs at a mean of 4.1 months as compared to the 9.7 months seen in their manual-group.

Gaster RN et al. stated their femto-PKs' suture removal occurred much earlier than in the manual-group.

Keratometry

Chamberlain et al. at an unstated timepoint, and Farid et al. at 1, 3, 6, 9 and 12 months follow-up, found no significant difference between their groups in keratometry.

Endothelial cell counts (ECC)

Bahar et al. found their femto-PKs had significantly superior endothelial cell densities (ECDs) at 12 months than their 90° side-cut trephine group, and significantly less endothelial cell loss than their manual-top-hat group at 12 months too.

Kamiya et al. at an unstated timepoint, and Levinger et al. at

Table 2
Visual acuity results of studies comparing femto-PK with manual-PK. Results in **bold** indicate a statistically significant difference was calculated by the study ($p < 0.05$).

BSCVA (LogMAR)							
Author	Group	1 month	3 months	6 months	12 months	9–20 months	24 months
Kamiya et al.	Laser	**0.58**	0.48	0.22			
	Manual	**0.93**	0.64	0.39			
Chamberlain et al.	Laser					0.265	
	Manual					0.341	
Daniel et al.	Laser top-hat						**0.30**
	Laser mushroom						**0.20**
	Manual						**0.40**
Gaster et al.	Laser		**0.46**	0.44			
	Manual		**0.69**	0.57			
Levinger et al.	Laser				0.31		
	Manual				0.32		
Bahar et al.	Laser				**0.32**		
	Manual (top-hat)				**0.53**		
	Manual				0.39		
Farid et al.	Laser	**0.26**	**0.20**				
	Manual	**0.54**	**0.36**				

12 months, both found no significant difference in ECD between manual and femto-PK. Kamiya et al. both found endothelial cell loss % age to not be significantly different at 12 months between manual and femto-PK.

Intraocular pressure (IOP)
Bahar et al. found no significant difference in IOP at 12 months between their two groups.

5. Femto-DALK vs manual-DALK

Studies were found comparing manual techniques to femtolaser-assisted deep anterior lamellar keratoplasty. Study characteristics are shown in Table 3.

5.1. Femto-Dalk indications

All studies investigated keratoconus patients only, apart from Shehadeh-Mashor et al. who included a minority of patients with ectasia and corneal scarring.

5.2. Femto-Dalk visual acuity

Visual acuity results are shown in Table 4.

Shehadeh-Mashor et al. also noted that their femto-DALKS had their greatest improvement in BSCVA between 0 and 3 months - their manual-DALKS achieved this between 3 and 6 months. Similarly, they found that between 0 and 3 months their femto-DALKs' postoperative BSCVA improvement was significantly better than their manual-DALKs. Maylugin et al. calculated a significantly higher rate of femto-DALK eyes (97.1%) reached a visual acuity lower than 0.5 LogMAR at 12 months, than manual-DALKs (71.4%).

5.3. Femto-dalk refraction

Three studies found significant refractive results in favour of the femtolaser. Li et al. and Maylugin et al. both found this occurred in corneal astigmatism at 12 months follow-up. Salouti et al. found at 12 months follow-up that the femto-DALKs had significantly less residual myopia, measured by spherical equivalent refraction, and a significantly more prolate cornea, measured by Q-values.

The other three studies found no significant difference in refractive or astigmatism outcomes at any timepoint.

5.4. Femto-dalk complications

Maylugin et al. noted that 85% of big-bubbles were achieved in their femto-DALKs, as opposed to 75% in their manual-DALKs. While not significant, they claim a sample size of 2.5 × would have given a significant result.

Salouti et al. Bleriot et al. and Shehadeh-Mashor et al. found a similar number of complications between both groups, with all three papers experiencing intraoperative and postoperative complications such as microperforations, incomplete big-bubbles and raised IOP. Salouti et al. had a much lower overall complication rate than the other two studies.

Li et al. encountered no complications in either group. Alio et al. did not report their complications.

5.5. Other outcomes

Suture removal
Bleriot et al. found their femto-DALKs had a significantly shorter duration of suture management than manual-DALKs (119 vs 470 days). Shehadeh-Mashor et al. found their manual-DALKs' sutures were removed significantly earlier than femto-DALKs.

Keratometry
Li et al. found at 12 months that their femto-DALKs had significantly lower keratometry. This was also seen in Salouti et al.'s results at 12 and 24 months in both keratometry and apical keratometry.

Bleriot et al. also measured keratometry and found no significant difference at any timepoint.

Endothelial cell counts
Bleriot et al. Li et al. (both measured at an unstated time) and Maylugin et al. (at 12 months) all found no significant difference for endothelial cell counts between their two groups.

Li et al. found that epithelial healing time was significantly faster in their femto-DALKs (three days) vs their manual-DALKs (six days).

Thickness of residual tissue
Maylugin et al. found no significant difference when this was measured at 12 months, while Salouti et al. and Li et al. both found at an unstated timepoint that their manual-DALKs had significantly thicker recipient bed thicknesses.

Table 3
Study characteristics of studies comparing femto-DALK with manual-DALK.

Study name	Author(s) and year published	N in FS-laser group (eyes)	N in control group (eyes)	Location	FS-keratoplasty graft profile	Surgical DALK method
Comparison between femtosecond laser mushroom configuration and manual trephine straight-edge configuration deep anterior lamellar keratoplasty	Shehadeh-Mashor et al. (2014) [25]	19	16	Canada	Mushroom	Anwar big-bubble or Melles technique depending on surgical preference
Comparison of 12-month anatomic and functional results between Z6 femtosecond laser-assisted and manual trephination in deep anterior lamellar keratoplasty for advanced keratoconus	A. Blériot et al. (2017) [26]	19	17	Nantes, France	Spherical with a 90*side cut	Anwar big-bubble technique
Femtosecond Laser Assisted Deep Anterior Lamellar Keratoplasty Outcomes and Healing Patterns Compared to Manual Technique	Jorge L. Alio et al. (2015) [27]	25	25	Alicante, Spain	Mushroom	Anwar big-bubble technique
Precisely Controlled Side Cut in Femtosecond Laser-Assisted Deep Lamellar Keratoplasty for Advanced Keratoconus	Li et al. (2016) [28]	94	100	Shandong, China	Spherical with a 90* side cut	Modified deep anterior lamellar keratoplasty
Deep anterior femtokeratoplasty in the treatment of patients with keratoconus: technique and results	Maylugin et al. (2017) [29]	34	33	Russia	Mushroom	Anwar big-bubble technique
Comparison between manual trephination versus femtosecond laser-assisted deep anterior lamellar keratoplasty for keratoconus	Salouti R, et al. (2019) [30]	391	469	Shiraz, Iran	Mushroom and decagonal	Modified Melles technique

Pachymetry
Bleriot et al. and Maylugin et al. both found no significant difference in pachymetry at any timepoint between their groups.

IOp
Bleriot et al. found no significant difference in IOP between their groups at 12 months.

Polymegatism/pleomorphism in corneal endothelium
Maylugin et al. found no significant difference between their groups in polymegatism/pleomorphism at 12 months.

Wound healing
Alio et al. utilised a measure for wound healing at the surgical site. This qualitative measurement was via a scoring system from an independent observer given to the surgical corneal wound at an unknown timepoint. Grade 0–4 could be assigned to each wound, grade 0 being a 'transparent scar' and grade 4 being a 'highly significant opacity with very significant cosmetic imbalance'. The closer a scar is to grade 4 the better in terms of healing activity. This study found healing to be significantly superior in the FS-group with more eyes at grade 3 and 4.

6. Femto-PLK vs manual-PLK

Four studies were found comparing manual techniques to femto-laser-assisted posterior lamellar keratoplasty. Study characteristics are shown in Table 5.

6.1. Femto-PLK indications

Einan-Lifshitz et al. only included patients with Fuch's. Heinzelmann et al. and Vetter et al. included both patients with Fuch's and bullous keratopathy. All eyes in Vetter and Pilger et al. were pseudophakic.

6.2. Femto-PLK visual acuity

Einan-Lifshitz et al. found no significant difference between their groups in BSCVA at 6 months nor in BSCVA improvement from 0 to 6 months. Pilger et al. also found no significant difference in BCVA at 3 months follow-up.

Heinzelmann et al. found that their MK-DSAEKs (microkeratome-DSAEKs) performed superior to their femto-DSAEKs in BSCVA when measured between 9 and 12 months. Vetter et al. also found their MK-DSAEKS to be superior in BCVA when measured at a follow-up mean of 8.5 months, and the femto-DSAEKs at 11.1 months.

6.3. Femto-PLK refraction

Einan-Lifshitz and Pilger et al. did not present any refractive outcomes. Heinzelmann et al. and Vetter et al. both found no significant difference in astigmatism at their previously stated follow-up times. Heinzelmann et al. also found no significant difference in spherical equivalent refraction.

6.4. Femto-PLK complications

Einan-Lifshitz et al. found that there were 4 graft failures in their manual-DMEKs, and none in their femto-DMEKs, with no graft rejections in either group. The manual-DMEKs had significantly higher graft-detachment post-surgery. Pilger et al. found more radial tears in their femto-DMEK group, and more graft detachments in their manual-DMEK group. Heinzelmann et al. found that 50% femto-DSAEK patients required regrafting to PK in a 20–200 day period postoperatively, significantly more than 12.2% of MK-DSAEKs. They also found that, as percentages, their femto-DSAEKs experienced more dislocations,

Table 4
Visual acuity results of studies comparing femto-DALK with manual-DALK. Results in **bold** indicate a statistically significant difference was calculated by the study ($p < 0.05$).

BSCVA (LogMAR)								
Author	Group	1 month	3 months	4 months	6 months	8 months	12 months	24 months
Shehadeh-Mashor et al.	Laser		**0.30**		0.30		0.23	
	Manual		**1.00**		0.31		0.30	
A. Blériot et al.	Laser			0.27		0.26	0.14	
	Manual			0.27		0.17	0.25	
Alio et al.	Laser	0.70			0.55		0.45	
	Manual	0.61			0.48		0.46	
Li et al.	Laser				**0.23**		**0.08**	
	Manual				**0.3**		**0.13**	
Maylugin et al.	Laser				**0.46**		0.34	
	Manual				**0.58**		0.46	
Salouti et al.	Laser						0.17	0.09
	Manual						0.18	0.11

rejections, glaucoma and poor wound interfaces.

Vetter et al. did not report complications.

6.5. Other outcomes

Endothelial cell counts

All four studies found no significant difference in endothelial cell counts or loss between their groups, at the previously stated follow-up times.

Morphology

Vetter et al. measured various morphological outcomes by pachymetry at an unstated timepoint. When measured via ultrasound they found that their femto-DSAEK corneas were significantly thinner than their MK-DSAEKs. When measured by OCT they found that there was no significant difference in corneal thickness. The OCT also showed that the graft thickness was not significantly different between the two groups, but the *host* thickness was significantly thinner in the femto-DSAEKs.

This study also calculated root mean square error (RMSE) as a measure of posterior surface irregularity, and they found that this was significantly increased in the femto-DSAEKs.

Pilger et al. found that there was increased variation in the size of their manual-DMEKs when compared with femto-DMEKs. The aimed diameter in both groups was to be 8.0 mm. With errors of 7% in the x-plane and 8% in y-plane for their manual-DMEKs, which was 1% for both in the femto-DMEKs, this led to significantly increased rhexis in the manual-DMEKs. Maximum distance between rhexis and transplant was not significant although the manual-DMEKs measurement for this nearly doubled that of the femto-DMEKs. A significantly greater surface area of denuded endothelium was also seen in their manual-DMEKs, although median area of endothelial overlap was not significantly different.

Risk of bias results

JBI case-control tools were used as all 17 studies were retrospective/partially retrospective case-controls, bar Pilger D and Vetter et al. who did not state this element of study design.

In appraisal the studies were especially weak in identifying/reporting confounding factors (and thus high confounding bias risk), with only seven studies seen as adequate. Only one of these seven studies gave strategies to deal with confounding factors, adding to confounding bias risk. The studies were also weak in recruiting comparable groups. Nine studies investigated groups with at least one significantly different baseline characteristic between study groups, and two further studies did not present pre-operative characteristics at all. This contributes to confounding and selection bias risk.

7. Discussion

7.1. Femto-PK

In visual acuity, there was a shared trend of superiority in the femto-PKs when compared to manual-PKs, with only two studies not finding a significant result supporting this. These significant results were seen in a 1–3 month period in three studies and in a 12 month + period in two studies, suggesting the visual acuity benefit of the femtolaser may be seen in both the short and long-term postoperatively. Of the studies with no significant visual acuity result, Levinger et al. only presented results at 12 months and perhaps a more comprehensive follow-up that included short or long-term timepoints would reveal any differences. Chamberlain et al's visual acuity results showed a trend of increasing in difference, in favour of the femtolaser, with p values continually decreasing in pinhole visual acuity until the last follow-up point at 15–18 months where $p = 0.0536$.

In refractive outcomes there was a trend shared in six of seven studies towards significantly superior outcomes in various refractive outcomes for the femtolaser. These significant outcomes were seen at follow-up points ranging from 1 to 20 + months. This suggests the femtolaser can improve refractive outcomes in the short and long-term. A recent, long-term observational study by Wade et al. found similar findings [35]. This is an important trend as astigmatism is the most common limiting visual factor post-manual-PK [36], and may require further treatment to improve. Intriguingly, given 15–31% of PK patients may experience postoperative astigmatism greater than 5D [36,37], Farid et al. identified that in a subgroup of patients who have pre-operative astigmatism > 5D, their femto-PKs showed a trend of decreasing mean astigmatism at each follow-up point, which was not seen in their manual-PKs. This suggests a potential greater benefit in those with high pre-operative astigmatism.

Kamiya and Chamberlain et al. suggested that short and long-term visual acuity and astigmatism benefit may be linked to the early suture removal. The three studies that assessed suture removal found that sutures in femto-PKs can be removed at a 4–6 month period

Table 5
Study characteristics of studies comparing femto-PLK with manual-PLK. FSL = Femtosecond laser.

Study name	Author(s) and year published	N in FS-laser group (eyes)	N in control group (eyes)	Location	Description of posterior lamellar surgery
Comparison of Femtosecond Laser-Enabled Descemetorhexis and Manual Descemetorhexis in Descemet Membrane Endothelial Keratoplasty	Einan-Lifshitz et al. (2017) [31]	17	89	Toronto, Canada	DMEK, investigating FSL when used for descemetorhexis
Visual outcome and histological findings following femtosecond laser-assisted versus microkeratome-assisted DSAEK	Heinzelmann et al. (2013) [32]	6	41	Germany	DSAEK, investigating FSL when used for graft preparation
Irregularity of the Posterior Corneal Surface After Curved Interface Femtosecond Laser-Assisted Versus Microkeratome-Assisted Descemet Stripping Automated Endothelial Keratoplasty	Vetter et al. (2013) [33]	8	14	Germany	DSAEK, investigating FSL when used for graft preparation
Exploring the precision of femtosecond laser-assisted descemetorhexis in Descemet membrane endothelial keratoplasty	Pilger et al. (2018) [34]	11	11	Berlin, Germany	DMEK, investigating FSL when used for descemetorhexis

postoperatively, as opposed to a 9–12 + month period for manual-PKs. Farid and Bahar et al. also linked superior visual outcomes to a more exact match between recipient and host. With early suture removal in femtolaser-keratoplasty being linked with a stronger wound interface [38] and/or increased wound surface area [3], both these effects can induce superior visual recovery by inhibiting graft torsion/dislocation [39].

Daniel et al. found superior spherical equivalent refraction at 24 months in their manual-PKs. They attributed this to specific femtolaser-applanation that became abhorrent in their mixed-disease cohort of eyes.

Complication rates showed a trend of mirroring manual-PKs in intraoperative safety, with no intraoperative complications seen for femto-PKs in any study. In postoperative complications, the most common trend appeared to be that the femtolaser gaves equivalent rates of postoperative-complications, as was seen in four studies. Kamiya et al. appeared to have less complications in their femto-PKs, perhaps due to their straight-edge, 90° cut used, the only study to use this profile. Statistical analysis would be useful to quantitatively analyse this.

Daniel et al. noted that their FS-mushroom group had the highest rate of complications in their study, with the majority of these being immune reactions, as was seen in a preceding observational study [40]. Daniel et al. attributed this to a wide anterior graft diameter [41] (mean diameter of anterior and posterior sections 8.3 ± 0.3 mm). Levinger et al. who also used FS-mushroom (mean anterior graft diameter 8.6 mm) did not experience these immune reactions, and so it would be useful to know if Daniel et al's mean anterior graft diameter exceeded 8.6 mm.

Bahar et al. found a femtolaser-favourable significant result in endothelial cell density that does not appear to have been reproduced in other studies – Levinger and Kamiya et al. found no significant differences. This is likely due to the top-hat shape used, allowing a wider posterior diameter of 8.5–8.7 mm to be grafted vs 7.75 m in their manual-PKs. Bahar et al. noted that, logically, this top-hat profile transplants more healthy donor ECs and leaves less host surface area for the donor ECs to cover.

7.2. Femto-DALK

There appear to be incongruent results in visual acuity, with three out of six included studies finding a significant result in favour of the femtolaser, and remaining studies finding no significant difference at any timepoint. The former three studies found the femtolaser provided significantly better visual acuity in a 3–12 month range of postoperative timepoints, indicating potential for faster visual recovery before manual-DALKs 'catch up' at later follow-up points. All three studies attributed this to the femtolaser's ability for accurate incisions that increase wound healing and strength, further reinforced when profiles are used to increase wound surface area. The paradigm of increased wound healing/strength is further backed up by Bleriot et al's significantly earlier suture removal with the femtolaser, mirroring results seen in femto-PK studies. And, Alio's wound healing results provide a significant, albeit qualitative, measure that further confirms superior wound healing with the femtolaser.

In refractive outcomes, again, three studies found a significant result (two in corneal astigmatism and the third in spherical equivalent refraction and Q-value), all at 12 months. In concordance with this, two out of these three studies (Li et al. and Salouti et al.) found significantly lower keratometry in follow-up. The ability of the femtolaser to produce decreased refractive error is particularly important in DALKs given the most common DALK indication is for keratoconic/ectatic disorders [42], which can cause unmanageable/progressive myopia and irregular astigmatism. Furthermore, astigmatism is one of the more common complications seen after keratoplasty for keratoconus [42–44].

It is unclear why some studies have found superior visual recovery with femto-DALK and some have not. Until recently, Li et al's study (which found significantly better visual acuity at 6 and 12 months, and astigmatism at 12 months) seemed particularly pertinent, with by far the largest sample size in femto-DALK interventional studies. Salouti et al.'s recent publication now provides an even larger sample size that found no significant visual acuity difference (although there were significantly better refractive outcomes), with results presented up to 24 months. They themselves suggest further investigation is warranted into whether femto-DALK provides superior visual recovery.

Three studies showed a trend of equivalent intraoperative and postoperative complication rates. Salouti et al. had a particularly low overall complication rate, the study attributed this to the surgeon's high experience in the surgery. However, a 2016 study by Khalil and Bor'I [45] compared intraoperative complications between 24 femto-DALKs and 40 manual-DALKs, using big-bubble technique. While not included in this review's results (they did not measure postoperative outcomes), it is of importance when discussing complication differences of femto-DALK vs manual-DALK. This study measured 19 overall intraoperative complications in their manual-DALKs, significantly more than just 3 seen in their femto-DALKs. These complications included decentred cuts, failure to form big-bubble, unplanned PK conversions and microperforations.

A limitation of DALK surgery is described as the technical challenge and extensive learning curve surgeons must endure when using the popular big bubble method [15,46–48]. The automatability and precision of the femtolaser is thought to ameliorate this [48]. Khalil and Bor'i show that clinical benefits may ensue, although of course the benefit seen depends on the surgeon's overall experience. It is noted there is certainly a trend that, subjectively, the operation is percieved to be easier with the femtolaser [25,26].

Maylugin et al. did note a higher success rate of big-bubble formations in their study, a result they claim to be significant if they had 2.5 × sample size, and in Lu et al.'s observational case-series [49], they believe the femtolaser accuracy gave their high rate of big bubble formation at 90.7%, greater than the commonly touted 80–90% seen in conventional Anwar big-bubble DALK [50], suggesting that clinical benefit can be seen, linked with increased ease of operation with femtolaser.

Li et al. intriguingly had no complications at all in either group, perhaps due to their own surgical method of DALK, termed 'modified DALK', that in previous studies has also had low intraoperative complications [51].

In other outcomes of interest, Salouti et al. and Li et al. noted significantly thicker recipient bed thickness in their manual-DALKs, which is associated with unwanted effects on refractive error [52]. This could reflect the femtolaser's precision to dissect to a specified point, or because both studies' surgeons started their studies' manual-DALKs earlier than their femto-DALKs and so had improved their surgical technique by the time femto-DALKs started. Li et al. linked their thinner recipient bed thickness in their femto-DALKs as to why the epithelium healed significantly earlier than their manual-DALKs.

It is noted Shehadeh-Mashor et al.'s suture removal results are incongruent with other studies reviewed, however this could be due to the fact they used different suturing techniques between the two groups.

7.3. Femto-PLK

In visual acuity results, the two interventional femto-DSAEK studies shared a finding that visual acuity is better when the donor globe is prepared using a microkeratome (MK-DSAEK). The two femto-DMEK studies both found no significant visual acuity difference between their groups, comparing femto-descemetorhexis vs. manual-descemetorhexis (manual-DMEK). Furthermore, the two femto-DSAEK studies both found no difference in measured refractive outcomes.

Poor visual acuity in femto-DSEK has perhaps limited research in this type of keratoplasty. Cheng et al's case-series [53] and clinical trial [54] also showed limited improvement in femto-DSEK BSCVA from a cumulative range of 3–12 months. This has been attributed to various features. High laser frequency and/or femtolaser cuts deep in the cornea can create a rougher interface than manual methods [15,55,56]. Indeed, Vetter et al. found a significantly increased RMSE in their femto-DSAEKS, a measure of corneal surface irregularity, showing this roughness may manifest itself postoperatively on the endothelium. The applanation of the femtolaser onto the eye may further aggravate the consistency of the cut [33,57]. Also, it has been suggested that high energy femtolasers can damage the endothelium [23].

Heinzelmann et al. found significantly more complications in their femto-DSAEK group, meaning that 50% needed a regraft to PK in 20–200 days post-operation. 37.5% of these were due to graft dehiscence that failed to readhere. They linked this with endothelial insufficiency after examining histological sections of their failed grafts, linking back to rough endothelial interface that can occur in femto-DSAEK.

The two femto-DMEK studies both followed a trend of decreased graft detachments in their femto-DMEKs. In Einan-Lifshitz et al. this was a significant difference. They also found that while rebubbling was needed in 17% of their manual-DMEKs, it was not needed at all in their femto-DMEKs. This is an important finding as graft detachment is the most common DMEK complication [58]. Both studies attribute this to the increased precision of the femtolaser, in terms of depth of cut in Einan-Lifshitz et al. and in predictability of graft diameter in Pilger et al. Although more radial tears were seen in Pilger et al. this did not appear to affect results or clinical outcomes. It is predicted that these would be avoided by doing a wider diameter descemetorhexis, which, unlike manual methods, would still confer a low risk of denudation as the femtolaser diameter is predictable, with less error.

7.4. Limitations

There was a low hierarchy of evidence - retrospective case controls formed the bulk of studies analysed. The majority of studies also had relatively small sample sizes, which limit statistical power and increase type I/type II error risk. Many studies only present relatively short-term follow-up of grafts that are planned to be lifelong, and an inherent caveat to any new interventional technology will be lack of information on long-term effects. Some potentially valuable studies could not be added due to language differences [59,60], less language constraints would have certainly allowed more studies to be included.

7.5. Future development

It becomes apparent in dissemination of femtolaser-assisted keratoplasty literature that there is wide scope for further research. There are a lot of clinical outcomes where the femtolaser has an advantage in some studies but not others. One must note that the nature of corneal transplantation makes the procedure intrinsically variable. There are biological, mechanical, immunological, environmental and surgical variables that may impact on a corneal transplant's success [27]. To control for these measures correctly powered, prospective, randomised controlled trials are warranted. Many experts have commented on this [4,18,19,21,30,40,49,61–63], but as of yet this does not appear to have been realised.

There is also scope to investigate other nuances in femtolaser-assisted keratoplasty. The femtolaser's dynamism has, in part, added to the variability around the surgery. There are many different profiles described each with their own suspected benefits. Prospective, in vivo studies that evaluate different graft profiles and their outcomes are warranted to substantiate some of the theorised benefits. The mushroom profile in particular, where a large anterior diameter potentially caused immune reactions in two papers that was not seen in other FS-mushroom studies, may need further investigation to avoid future complications.

In DALK surgery, the femtolaser adds further paradigms. The femtolaser's uniform and precise recipient cut grafts allow an accurate channel to gauge depth at which to inject air [26,27,48,64] – this is what likely influenced the significant results by Khalil and Bor'i. Additionally, as stated previously, it is common opinion that it is subjectively easier for surgeons. Formal investigation of individual learning curves may reveal a measured advantage for the femtolaser, as has been investigated in conventional big-bubble DALK [65,66].

Anwar big-bubble techniques vs Melles has long been investigated in conventional-DALK research. A clinical trial in 2013 revealed no difference in main postoperative outcomes. A clinical trial comparing the two techniques using the femtolaser would further quantify any advantage the femtolaser has in big-bubble DALKs.

A number of papers comment on the femtolaser's expense [28,67,68], and that medico-economic analysis is warranted [26]. This has been done in femto-DSAEKs, which found it as less cost-effective when compared with manual-DSAEK and manual-PK [69]. High costs and impracticality (some models are large and immobile and thus required patient moving to the operating room after cuts were done) are some of the factors likely preventing uptake in public healthcare.

However, its high cost may be outlaid in future as more companies enter and compete on the market, driving costs down. Many of the older studies used the IntraLase, but other machines are growing in popularity [70]. Each vary, with different spot sizes and pulse duration, rate and energy [71]. The technology continues to develop to become more practical, with many suggestions for improvement realised. Soong and Malta's 2009 review [72] hoped for more portable systems, by 2011 mobile femtolasers came onto the market [71]. The hope for models able to perform cataract, corneal and refractive surgery on the same machine has also been documented [15,19], as of 2018 some models can do this [48] – which should ease financial burden.

There is still further development to be done. It has been commented on previously in discussion that the femtosecond applanation process can induce unwanted effects. A further caveat to the applanation process is the subsequent rise in IOP may prevent the use of the femtolaser in emergency scenarios [15]. Some studies suggest a change in this process, perhaps requiring no contact to cornea at all [26,32–34].

Increased wound healing and strength with the femtolaser in PK and DALK is certainly supported by earlier suture removal results and Alio et al's results. A further measure that would link with this would be corneal biomechanical stability, as measured by corneal hysteresis and resistance factor, which was not measured and compared in any of the studies included. It was commented on in a *meta*-analysis of corneal biomechanical stability post-DALK that there is little in vivo femto-DALK data measuring this [73].

8. Conclusion

In conclusion, comparative investigations of the femtolaser in penetrating keratoplasty shows a trend of significantly improved visual outcomes, in the short and long term. Complication rates are similar, and the top-hat shaped femto-PK may significantly lower endothelial cell loss when compared with conventional PK, unlike other profiles. Comparative investigations of the femtolaser in deep anterior lamellar keratoplasty showed that in some studies the femtolaser performs better in visual outcomes 3–12 months post-operation, and sometimes has no difference throughout follow-up. There is evidence intraoperative complication rates are decreased, and of significantly increased wound healing activity with the femtolaser. Earlier suture removal is an advantage in PK and DALK. The use of the femtolaser in DMEK appears promising in reducing graft detachment. The use of the femtolaser in DSAEK appears limited when compared with microkeratome for graft preparation.

It is important to consider the low hierarchy of evidence and a trend showing increased risk of confounding and selection bias in the studies included in this review. However, there is evidence the precision of the femtolaser appears can produce superior visual recovery and/or reduced complications in PK, DALK and DMEK. There is wide scope for further research to substantiate the advantages of femtolaser brings and provide a superior hierarchy of evidence on which to base clinical opinions and decisions on.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Contributorship statement

This paper was an output from first author, JA's integrated BMedSci degree. Author JA discussed with lead author, PH and co-author, AK on the research question and establish the PICOD inclusion and search criteria. JA, PH & AK screened papers based on title and abstract and obtained full texts to undergo full text screening. Additional input and critique was provided by co-author to include new search stratgies and further information, JM. The JBI quality assessment tool was used on full text papers and in the final cohort of publications, these were used to create and complete data extraction tables.

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Appendix A

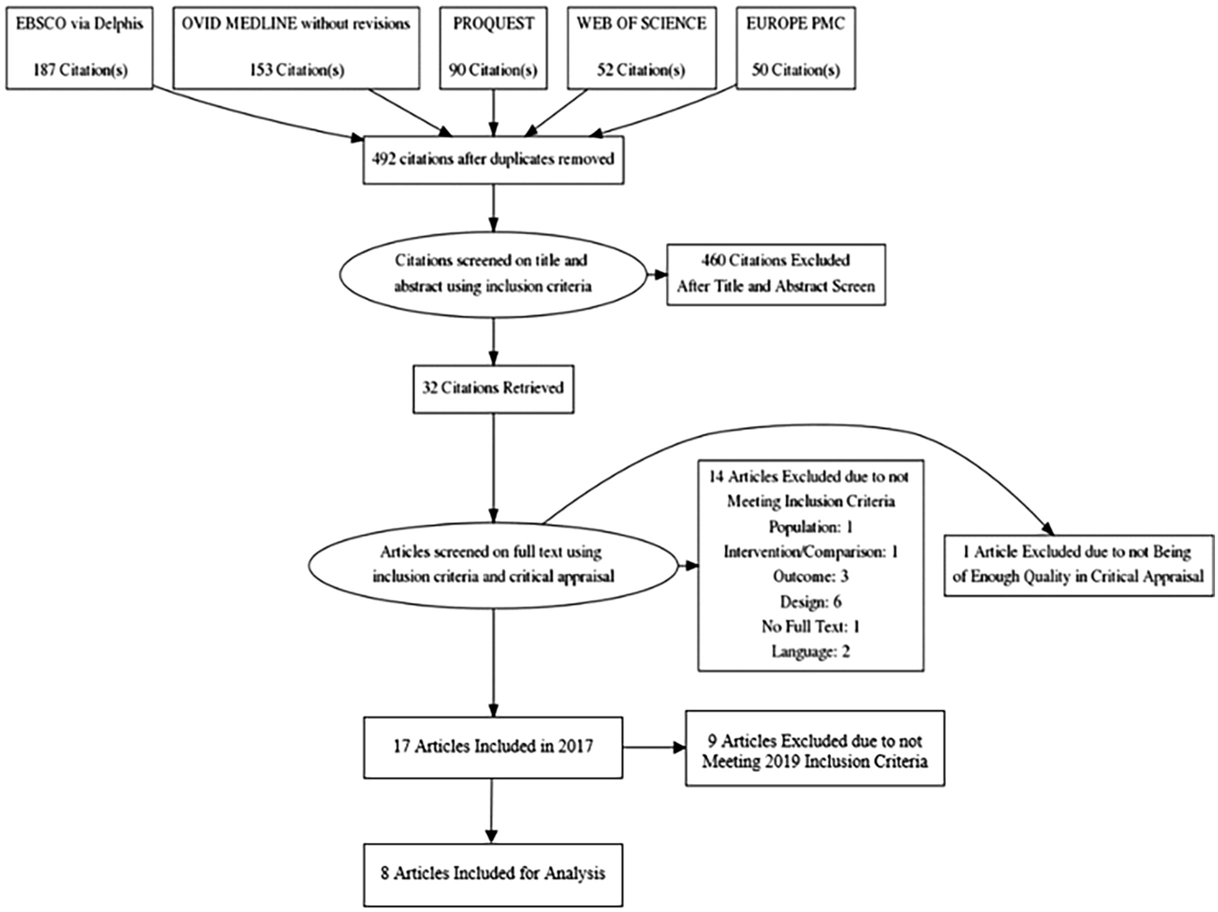

Fig. A1. The 2017 identification process for this systematic review, adapted from the reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. The 2019 PICOD criteria was then applied to the studies found in this identification process.

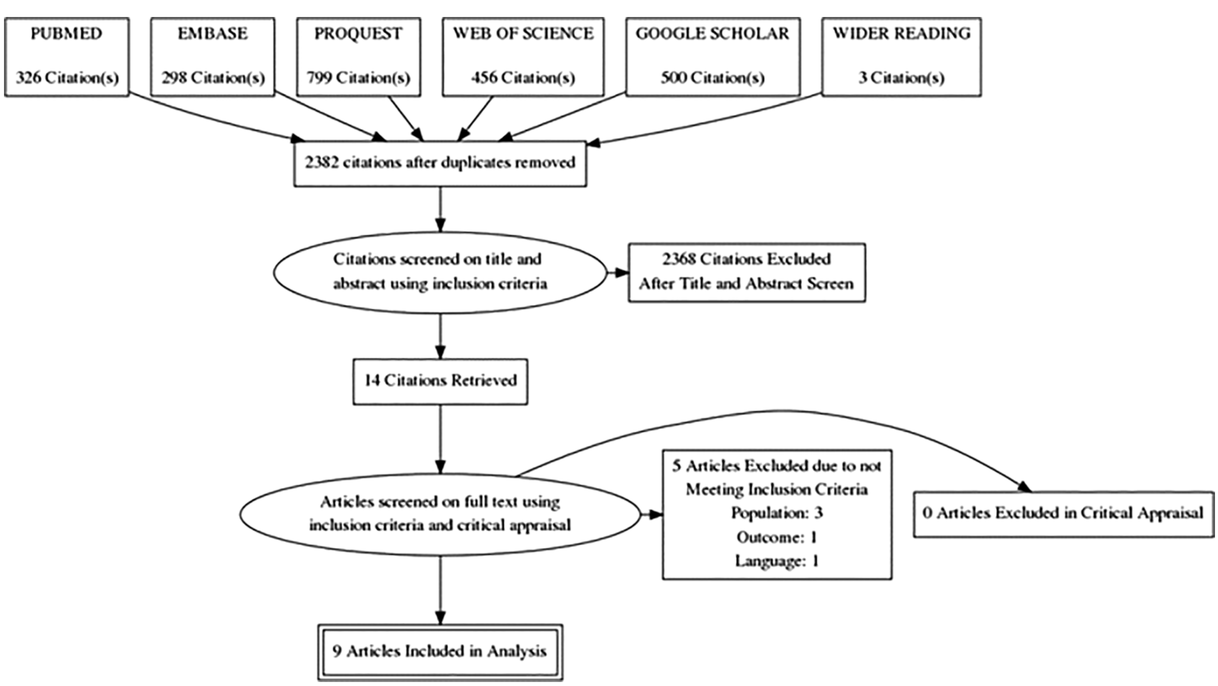

Fig. A2. The 2019 identification process for this systematic review, adapted from the reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

Appendix B

Table B1
Search strategy used for electronic databases, apart from Europe PMC. This search strategy was used in both 2017 and 2019 searches.

Search number	Search term
1	Keratoplasty or corneal transplantation
2	Knife
3	Laser?
4	Femtolaser or femtosecond
5	1 and 2 and 3
6	trephine
7	1 and 3 and 6
8	Cornea?
9	1 or 8
10	2 and 3 and 9
11	3 and 6 and 9
12	3 or 4
13	1 and 2 and 12
14	9 and 12
15	6 and 9 and 12
16	2 and 9 and 12

Appendix C

Table C1
PICOD criteria used in 2017 search. The studies found with these criteria in 2017 were overridden by 2019 PICOD criteria for this review.

Population	Adults undergoing any type keratoplasty, for any indication.
Intervention	Femtolaser-assisted keratoplasty must be applied to at least one group in the study.
Comparison	Same keratoplasty procedures as done by trephine OR same FS-laser procedure with a different depth of keratoplasty.
Outcomes	Any patient centred outcomes.
Design	Randomised and non-randomised studies were to be included. Interventional and observational studies were to be included.

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