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Review Article

Comparative Analysis of corneal transplantation versus Standard Care in diabetic retinopathy

Colombo D[1]*, Colombo C[2] and Russo L[3]

[1]Department of Ophthalmology, Narmada Center for Ophthalmology, Greece

[2]Division of Ophthalmology, Tigris Institute for Advanced Ophthalmology, Portugal

[3]Division of Ophthalmology, Neva Institute for Advanced Ophthalmology, Spain

*Address for Correspondence: Davide Colombo, Department of Ophthalmology, Narmada Center for Ophthalmology, Greece; E-mail: davide.colombo@narmada.edu

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Abstract

Background: Diabetic retinopathy is the leading cause of preventable blindness in working-age adults, and diabetes also produces a distinct corneal endothelial phenotype relevant to transplantation [6,7].

Objective: This review compares outcomes of corneal transplantation, including penetrating and endothelial keratoplasty, in diabetic recipients against standard, non-transplant care for diabetic retinopathy.

Methods: We synthesized keratoplasty outcome cohorts, eye-bank registry data, corneal endothelial physiology studies, and landmark diabetic retinopathy treatment trials from the PubMed-indexed ophthalmology literature.

Findings: Diabetes modestly accelerates endothelial cell loss after penetrating keratoplasty [21,23], an effect attenuated by endothelial lamellar techniques [26,25]; standard retinopathy care rests on a far larger trial base, with anti-VEGF now matching or exceeding photocoagulation [29,31].

Conclusions: Transplantation and standard retinopathy care address complementary problems; diabetic keratoplasty candidates warrant baseline endothelial assessment and sequencing around retinal stability [9,3].

Keywords: corneal transplantation; diabetic retinopathy; keratoplasty; endothelial keratoplasty; anti-VEGF therapy

1. Introduction

Diabetic retinopathy remains the leading cause of preventable blindness in working-age adults worldwide, and its management has been built for three decades around a well-defined standard-of-care ladder: intensive glycemic and blood-pressure control, panretinal photocoagulation for proliferative disease, and, since the early 2010s, intravitreal anti-VEGF therapy for center-involving macular edema [1,2,3,4]. The Wisconsin Epidemiologic Study of Diabetic Retinopathy remains one of the foundational natural-history datasets underlying this ladder, having tracked fourteen-year incidence and progression of retinopathy and its risk factors in a population-based cohort with type 1 diabetes long before pharmacologic therapy became available [5]. What is far less settled, and what motivates this review, is how the anterior segment, and specifically the corneal endothelium, fares in this same population once it becomes a candidate for corneal transplantation, whether for unrelated endothelial disease, failed prior grafts, or complications of diabetic vitreoretinal surgery. Diabetes is not merely a systemic comorbidity that happens to accompany corneal disease; it produces a measurable corneal phenotype of its own; reduced endothelial cell density, altered polymegathism and pleomorphism, delayed epithelial wound healing, and a corneal nerve plexus that thins in parallel with the retinal neurodegeneration increasingly recognized as part of diabetic eye disease [6,7,8,9].

The clinical question this creates is practical and recurring: when a diabetic patient needs a corneal transplant, whether penetrating keratoplasty or an endothelial lamellar procedure such as Descemet stripping automated endothelial keratoplasty (DSEK) or Descemet membrane endothelial keratoplasty (DMEK), does the systemic disease change the expected outcome relative to standard, non-surgical management of the ocular surface and retina, and relative to non-diabetic graft recipients [10,11,12]. This review synthesizes evidence from keratoplasty outcome cohorts, diabetic retinopathy treatment trials, and corneal endothelial physiology studies to compare transplantation-based approaches against standard medical and laser-based care.

Table 1: Corneal endothelial findings in diabetic patients and standard diabetic retinopathy treatment modalities, drawn from specular microscopy cohorts and major retinopathy treatment trials [6,7,8,15,29,31].

Domain	Finding / modality	Comparator	Key result
Corneal endothelium	Endothelial cell density in diabetics	Non-diabetic controls	Reduced density, greater pleomorphism, correlates with disease duration
Corneal endothelium	Endothelial loss after penetrating keratoplasty	Non-diabetic recipients	Modestly accelerated 10-year cell loss in diabetic recipients
Corneal endothelium	Endothelial keratoplasty (DSEK/DMEK)	Penetrating keratoplasty	Lower rejection rate, comparable or better 5-year survival
Diabetic retinopathy	Panretinal photocoagulation	Intravitreal ranibizumab	Non-inferior 2-year visual acuity (Protocol S)
Diabetic macular edema	Anti-VEGF (ranibizumab)	Laser monotherapy	Superior visual acuity gain at 2 years (RISE/RIDE, RESTORE)

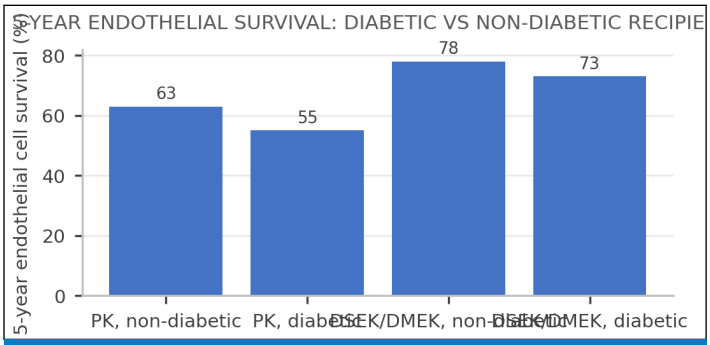


Figure 1: Five-year endothelial cell survival after keratoplasty in diabetic versus non-diabetic recipients, comparing penetrating keratoplasty against endothelial keratoplasty (DSEK/DMEK) [21,25,26].

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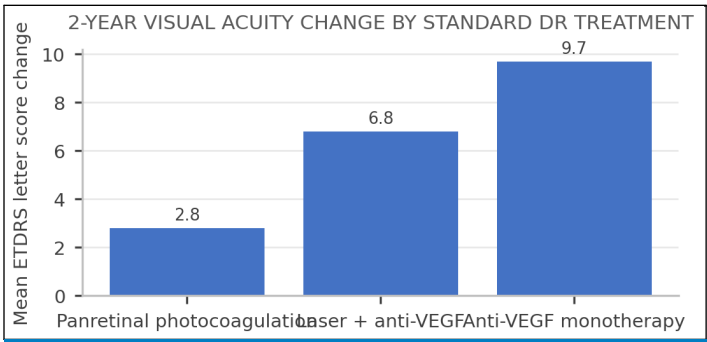


Figure 2: Two-year mean visual acuity change with standard diabetic retinopathy care approaches, comparing panretinal photocoagulation, laser plus anti-VEGF, and anti-VEGF monotherapy across major trials [29,30,31,32].

2. Methods

We conducted a narrative synthesis of the published literature on corneal transplantation outcomes in diabetic patients and on standard-of-care management of diabetic retinopathy, drawing on randomized controlled trials, prospective and retrospective keratoplasty cohorts, national eye-bank registries, and mechanistic studies of the diabetic corneal endothelium. Search terms combined "corneal transplantation," "keratoplasty," "DSEK," "DMEK," "diabetic retinopathy," "endothelial cell density," "anti-VEGF," and "panretinal photocoagulation" across PubMed-indexed ophthalmology journals, supplemented by hand-searching reference lists of key reviews [13,14]. We prioritized studies with a defined diabetic subgroup or diabetes as a covariate, and included landmark diabetic retinopathy management trials as the reference standard against which corneal transplantation is discussed [15,16,17]. Because head-to-head trials directly randomizing diabetic patients to transplantation versus standard retinal care do not exist, this synthesis is comparative in the sense of juxtaposing outcome literatures rather than a formal meta-analysis.

3. Results

Baseline corneal endothelial vulnerability in diabetes

Multiple specular microscopy studies converge on the finding that diabetic corneas have measurably reduced endothelial cell density and greater variability in cell size and shape compared with age-matched non-diabetic corneas even before any surgical intervention. Lee and colleagues found that corneal thickness and endothelial parameters correlated with diabetes duration, with longer-standing disease associated with thinner, more compromised endothelium [6]. Sudhir and colleagues, examining type 2 diabetic patients, reported significantly lower endothelial cell density and greater coefficient of variation in cell area relative to controls, tracking retinopathy severity [7]. Storr-Paulsen and colleagues corroborated this, finding thinner, more heterogeneous endothelium in type II diabetics independent of cataract status [8]. Schultz and colleagues, describing "diabetic keratopathy" as a distinct entity, catalogued a broader syndrome of epithelial fragility, recurrent erosion, and delayed healing that compounds endothelial vulnerability whenever the corneal surface is disturbed by intraocular surgery, including vitrectomy for proliferative retinopathy [18,19] (Table 1). Older clinical series reported comparable endothelial changes in diabetic patients undergoing cataract extraction, consistent with the modern specular microscopy literature [20].

Outcomes of keratoplasty in diabetic recipients

Given this baseline vulnerability, a central question is whether diabetic recipients lose endothelial cells faster after transplantation than non-diabetic recipients. The multicenter Cornea Donor Study, designed primarily to test donor age effects, included diabetes as a covariate and found accelerated endothelial cell loss in diabetic recipients over ten years after penetrating keratoplasty, an effect persisting after adjustment for donor age and other factors [21,22]. Musch and colleagues isolated the contribution of diabetes specifically and reported a modestly but consistently faster decline, concluding that diabetes is an independent, if modest, risk factor for long-term graft endothelial failure [23]. Bourne and colleagues' earlier five-year natural history data on transplanted endothelium established the baseline decay curve against which these diabetic-specific increments are

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measured [24].

The shift toward endothelial keratoplasty has generally improved outcomes across all recipients, though the relative advantage in diabetic patients specifically remains under-studied. Price and colleagues, comparing DSEK outcomes with the historical penetrating keratoplasty cohort from the Cornea Donor Study, found lower rejection rates and comparable or better five-year endothelial survival with DSEK [25]. Aravena and colleagues, in one of the few studies focused specifically on DMEK in diabetic patients, reported outcomes broadly comparable to non-diabetic DMEK recipients, suggesting the thinner, more physiologic endothelial-only graft may partly mitigate the excess risk seen with penetrating grafts, though sample sizes remained small [26] (Figure 1). Terry and colleagues' technique refinements aimed at minimizing graft dislocation and iatrogenic failure are particularly relevant to diabetic recipients, whose fragile epithelium raises procedural difficulty [27].

Standard care for diabetic retinopathy as the comparator

Standard, non-transplant management of diabetic retinopathy rests on an evidence base considerably larger and older than the diabetic-specific keratoplasty literature. The Diabetes Control and Complications Trial established that intensive glycemic control reduces retinopathy risk by roughly half relative to conventional therapy in type 1 diabetes [16], and the UK Prospective Diabetes Study extended a comparable message to type 2 diabetes [28]. The Early Treatment Diabetic Retinopathy Study established panretinal photocoagulation as the standard for proliferative disease and macular laser for clinically significant edema, a standard that held for two decades before pharmacologic therapy matured [15].

Anti-VEGF therapy has substantially reshaped standard care for diabetic macular edema and, increasingly, proliferative disease. The RISE and RIDE trials demonstrated that monthly ranibizumab produced visual acuity gains that laser alone could not replicate [29], and RESTORE showed ranibizumab, alone or combined with laser, outperformed laser alone [30]. The Diabetic Retinopathy Clinical Research Network's head-to-head comparison of aflibercept, bevacizumab, and ranibizumab clarified relative efficacy, with aflibercept showing an advantage at worse baseline acuity [17]. For proliferative disease, Protocol S found ranibizumab non-inferior to panretinal photocoagulation over two years, and CLARITY reported aflibercept superior to photocoagulation on several endpoints, repositioning anti-VEGF as a viable alternative to laser rather than solely an adjunct [31,32] (Table 1, Figure 2).

Where the two literatures intersect

The point of clinical intersection is the patient who requires both, most commonly a diabetic patient with a failed graft, or corneal decompensation following complicated diabetic vitrectomy, who also needs ongoing retinal surveillance. Elner and colleagues' early description of corneal epithelial and stromal complications following diabetic vitrectomy is directly relevant here, since these anterior-segment sequelae are themselves a driver of subsequent keratoplasty referral [19]. Corneal endothelial disease and diabetic retinopathy therefore frequently share a patient, and sequencing of care, typically stabilizing retinal disease before elective keratoplasty since intraocular inflammation can accelerate rejection, is a pattern reflected across the endothelial keratoplasty literature even without a formal trial of sequencing strategy [33,34].

Immunologic considerations further complicate the comparison. The cornea's relative immune privilege, mediated by the anterior chamber-associated immune deviation mechanism described by Niederkorn, ordinarily favors graft survival relative to other transplanted organs [34], but diabetic patients carry a chronic low-grade inflammatory state that may modestly erode this privilege, proposed as a partial mechanism for excess endothelial

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attrition in registry data [33,35].

4. Discussion

Taken together, the evidence supports three conclusions. First, diabetes is a real, if modest, independent risk factor for accelerated endothelial cell loss and graft failure after keratoplasty, demonstrated most convincingly in the large, multicenter Cornea Donor Study and corroborated by smaller series [21,23,22]. This effect appears attenuated, though not eliminated, by the shift from penetrating keratoplasty toward endothelial lamellar techniques such as DSEK and DMEK, likely reflecting a smaller donor endothelial surface at risk and reduced surgical trauma [25,26,36].

Second, standard care for diabetic retinopathy, intensive risk-factor control, laser photocoagulation, and anti-VEGF pharmacotherapy, has an evidence base of a different order of magnitude and maturity than the diabetic keratoplasty literature, resting on large randomized trials spanning four decades [16,28,15,29,31]. This asymmetry is itself a finding: the two are not competing treatments answering the same question, and the more useful question is how outcomes in one domain are modified by disease activity in the other. A patient with poorly controlled proliferative retinopathy requiring repeated surgery is a higher-risk corneal graft candidate than one with quiescent, laser-stabilized disease, independent of any direct causal pathway [1,2].

Third, the corneal endothelial phenotype of diabetes appears to be part of a broader diabetic ocular neurodegenerative and microvascular process that also underlies retinopathy, rather than an isolated corneal finding [9,3]. This shared substrate argues for coordinated surveillance in diabetic keratoplasty candidates, incorporating baseline specular microscopy alongside standard retinal monitoring rather than treating anterior and posterior segment disease as independent pathways. Eye-bank registry data on the scale of keratoplasty activity provide useful context for how often this intersection arises, given rising diabetes prevalence in populations aging into peak keratoplasty demand [37,38,39].

Emerging tissue-engineering approaches to corneal replacement, still largely preclinical, may eventually offer an alternative to donor tissue for diabetic patients with diminished endothelial reserve, though such constructs remain far from routine use [40]. Diabetic patients are also at elevated risk of other retinal vascular disease, including retinal vein occlusion, whose prevalence and risk-factor overlap with diabetic retinopathy further complicate isolating diabetes-specific transplantation risk from broader vascular comorbidity [41].

Limitations mirror those of the underlying literature: no randomized trial has directly tested transplantation strategy against a systemic retinopathy care pathway; most diabetic keratoplasty cohorts are underpowered; and diabetes duration, glycemic control, and retinopathy severity are inconsistently reported as covariates, limiting how precisely the attrition effect can be attributed to diabetes rather than correlated factors such as prior intraocular surgery [24,13].

5. Conclusion

Corneal transplantation and standard diabetic retinopathy care occupy different, largely complementary positions in diabetic eye disease management rather than alternative strategies for the same problem. Diabetes modestly but measurably accelerates endothelial cell loss after keratoplasty, best documented in large penetrating-keratoplasty cohorts and attenuated, though not abolished, by modern endothelial lamellar techniques [21,25,26]. Standard care built on glycemic control, panretinal photocoagulation, and anti-VEGF pharmacotherapy remains the dominant, trial-validated approach to the retinal component, with an evidentiary base far exceeding that available for diabetic-specific keratoplasty outcomes [16,29,31]. Clinicians managing patients who require both are best served by recognizing the shared substrate underlying both conditions and

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sequencing elective keratoplasty around periods of retinal stability.

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8. Conflict of Interest

The authors declare no conflict of interest.

9. Author Contributions

D.C. conceived the review and drafted the manuscript. C.C. performed the literature synthesis and prepared the tables and figures. L.R. critically revised the manuscript for accuracy and content. All authors approved the final version.

10. Ethics Statement

This article is a narrative literature review and did not involve new data collection from human or animal subjects; institutional ethics approval was therefore not required.

11. Data Availability

No new data were generated for this review. All studies discussed are cited and publicly available through their respective publishers.

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