

wound leaks or tissue incarceration, hypotony, significant postoperative inflammation, abnormal or absent endothelium, and vascularized corneal stroma.¹⁰ Treatment usually involves resection with or without adjunctive cryotherapy. Prognosis can be poor given the risk of recurrence, refractory glaucoma, and corneal decompensation.¹⁰

Epithelial downgrowth has been reported following deep lamellar endothelial keratoplasty.¹¹ Culbertson¹² reported a single case of presumed epithelial downgrowth within a lamellar graft interface following DSAEK, although there was no histopathologic confirmation. Our case provides histological confirmation of epithelial downgrowth after a DSAEK procedure.

The introduction of ectopic host epithelial cells in our patient may have occurred via attachment to the donor tissue at the time of insertion. Alternatively, the initiation of downgrowth may have occurred postoperatively via communication with an external source of corneal or conjunctival epithelial cells. The epithelial-lined cleft between the posterior stroma and Descemet's membrane seen on histopathologic examination demonstrates invasion of epithelial cells into this posterior plane as well as in the stromal interface. This finding corresponds with clinical evidence of downgrowth at these locations (Figure 1A and B) and also favors an invasive, postoperative downgrowth process as opposed to an intraoperative implantation mechanism. Of note, there was no fistula in this patient to delineate the site of epithelial invasion.

Review of our patient's history reveals multiple risk factors associated with epithelial downgrowth. She underwent several operations and had a prolonged course of anterior chamber inflammation after DSAEK. Previous research in rabbit corneas has suggested that a healthy endothelium can prevent epithelial migration by contact inhibition, and when the endothelium is denuded, the epithelium can rapidly cover Descemet's membrane.¹³ In DSAEK, the diseased donor endothelium is purposefully removed, and healthy donor tissue is stored in transport media and then surgically implanted into the host eye. This provides significant opportunities to transmit host or donor epithelial cells into the eye. Furthermore, the most common complication of DSAEK is spontaneous donor detachment, requiring reattachment by injection of an air bubble to reappose the donor and recipient tissues.¹⁴ Such periods of absent Descemet's membrane and endothelium along the recipient's posterior corneal surface may encourage epithelial proliferation and migration. As DSAEK continues to gain popularity, the consideration of epithelial downgrowth in the differential diagnosis of localized opacification of the interface or posterior corneal surface may gain relevance. In addition, corneal imaging modalities such as in vivo confocal microscopy can provide valuable diagnostic information to inform clinical decision making in these challenging cases.

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Is a History of Diabetes Mellitus Protective Against Developing Primary Open-angle Glaucoma?

In 2002, the Ocular Hypertension Treatment Study¹ (OHTS) reported baseline factors that increased the risk for developing primary open-angle glaucoma (POAG): older age, a larger vertical cup-disc ratio, higher intraocular pressure, greater Humphrey visual field pattern standard deviation, and a thinner central corneal measurement. A history of diabetes mellitus at baseline appeared to be protective against developing POAG. Six of the 191 participants (3.1%) who reported diabetes mellitus at baseline developed POAG compared with 119 of the 1427 participants (8.3%) who did not (multivariate hazard ratio, 0.37; 95% confidence interval, 0.15-0.90). This finding was unexpected and contradicted most of the literature on risk factors for POAG.²⁻⁴

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The 2002 article acknowledged methodological issues in the OHTS that might account for this finding. Participants were classified at baseline as having a positive

Table. Hazard Ratios for Developing Primary Open-angle Glaucoma for Various Definitions of Diabetes Mellitus

Diabetes Mellitus Definition	Diabetes Mellitus Classification of Participant	Participants Developing POAG, No. (%) ^a	Univariate HR (95% CI)	Multivariate HR (95% CI) ^b
High sensitivity and low specificity	Yes	409 (6)	0.70 (0.45-1.10)	0.76 (0.50-1.20)
	No	1227 (8)		
Moderate sensitivity and moderate specificity	Yes	277 (6)	0.63 (0.37-1.07)	0.73 (0.43-1.24)
	No	1036 (9)		
Low sensitivity and high specificity	Yes	256 (7)	0.84 (0.51-1.39)	0.84 (0.51-1.39)
	No	1057 (9)		

Abbreviations: CI, confidence interval; HR, hazard ratio; POAG, primary open-angle glaucoma.

^aDifferences in sample size reflect missing data.

^bThe multivariate model includes the diabetes mellitus classification, baseline age, baseline intraocular pressure, baseline vertical cup-disc ratio, baseline pattern standard deviation, and central corneal thickness.

history of diabetes mellitus if they responded yes to the question, “Has a doctor ever told you that you have . . . diabetes, or sugar in the blood?” A positive history of diabetes mellitus was not corroborated by record review, blood tests, or medication use. Underascertainment of diabetes mellitus could result from underdiagnosis as well as underreporting by participants. In addition, OHTS entry criteria excluded diabetic patients with any retinopathy so that participants with diabetes mellitus were likely to be atypical.⁵

Methods. Starting in February 2003, after approval by the Data and Safety Monitoring Committee and local institutional review boards of participating clinics, the OHTS began collecting more detailed information about whether participants had been diagnosed with diabetes mellitus and what treatments they were receiving. We reran the same Cox proportional hazards prediction model for POAG using the same data set of baseline predictors and outcomes and varying only the definition of diabetes mellitus. No blood tests or corroborating record reviews were performed. The different definitions of diabetes mellitus, all of which were based on participant self-report, varied in sensitivity and specificity as follows:

- High sensitivity and low specificity: At baseline or follow-up, the participant responded yes to the question, “Has a doctor ever told you that you have any of the following conditions . . . diabetes or sugar in the blood?”
- Moderate sensitivity and moderate specificity: The participant responded yes that “a doctor or health professional recommended a special diet to lower your blood sugar.”
- Low sensitivity and high specificity: The participant responded yes that they were currently receiving “insulin” or “diabetic pills to lower your blood sugar.”

Results. During follow-up, 409 participants responded that a doctor had told them they had diabetes or sugar in the blood, as compared with 191 participants who answered yes to the same question at baseline (**Table**). All of the 191 participants who had reported a positive history of diabetes mellitus at baseline also reported a positive history at 1 or more follow-up visits. In updated univariate and multivariate analyses, a history of diabetes mellitus was not statistically significantly predictive for the development of POAG for all of the 3 definitions tested.

Comment. The protective effect of a history of diabetes mellitus for the development of POAG reported in the 2002 OHTS prediction model¹ was not supported in univariate or multivariate analyses using updated self-reported data on diabetes mellitus history and its treatment. We believe the difference from the 2002 article reflects more complete ascertainment of diabetes mellitus. Many more participants reported a positive history of diabetes mellitus during follow-up than at baseline. The results of these re-analyses are consistent with several previous studies^{2,3} reporting that diabetes mellitus either increased the risk of developing POAG or had no effect.

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