

Recurrent keratoconus: an analysis of breaks in Bowman's layer in corneal grafts

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ABSTRACT

Objective To study in a masked fashion whether an objective histological feature associated with keratoconus (KCN) occurs in donor corneas in eyes originally receiving a corneal graft for KCN.

Methods Two ocular pathologists performed a retrospective masked histological analysis of slides from donor buttons recovered from 21 eyes with a history of KCN undergoing repeat penetrating keratoplasty (failed-PK-KCN), 11 eyes that underwent their first PK due to KCN (primary KCN), and 11 eyes without history of KCN which underwent PK for other conditions (failed-PK-non-KCN). Breaks/gaps in Bowman's layer served as the pathological feature indicative of recurrent KCN.

Results Breaks in Bowman's layer were present in 18/21 (86%) of the failed-PK-KCN group, 10/11 (91%) of the primary KCN group, and in 3/11 (27%) of the failed-PK-non-KCN group. Pathological evidence suggests that the prevalence of breaks is significantly higher in grafted patients with a history of KCN than non-KCN controls (OR: 16.0, 95% CI 2.63 to 97.2, Fisher's exact test $p=0.0018$) with a conservative Bonferroni criterion of $p<0.017$ to account for multiple group comparisons. There was no statistically significant difference found between the failed-PK-KCN and primary KCN groups.

Conclusions This study provides histological evidence that breaks and gaps in Bowman's layer, consistent with those found in primary KCN, may develop within the donor tissue in eyes with a history of KCN.

INTRODUCTION

There have been many efforts to better understand the molecular events and cytohistological changes responsible for keratoconus (KCN).¹ Abnormal synthesis of glycosaminoglycans^{2,3} or collagen,⁴ as well as an increased degradation of extracellular matrix by corneal cells,^{5,6} constitutional⁷ and environmental⁸ factors, mechanical eye rubbing⁹ and hormonal and metabolic imbalances¹⁰ has been suggested as potential mechanisms that cause KCN and its progression. Histopathologic and ultrastructure features of KCN have been characterised in native keratoconic corneas.^{11,12} Breaks in Bowman's layer

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previously published observations of recurrent keratoconus in keratoplasties demonstrated breaks in Bowman's layer. However, these studies were published primarily as case reports. Recurrent keratoconus had been observed in grafts that were at least 10 years old.

WHAT THIS STUDY ADDS

⇒ This study is a retrospective masked histological comparison of failed corneal transplants of patients with a history of keratoconus and without keratoconus. This study shows that breaks in Bowman's layer occur in failed grafts with a history of keratoconus, and it was statistically significant when compared with grafted tissue for other non-keratoconus diagnoses. Furthermore, breaks are found in grafts that were less than 10 years old with nearly 50% occurring less than 5 years post-transplantation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study showed that histological findings consistent with keratoconus occur in corneal transplants in patients with keratoconus within a few years post-transplantation. This suggests that keratoconus is an active condition that has pathological findings found in the host and the graft. Careful observation of changes in keratometric parameters indicative of corneal ectasia should be monitored.

that cause upgrowth of the stroma and downgrowth of the epithelium have been reported in KCN.^{13–16} Moreover, some studies have also shown the presence of ectatic changes in corneal grafts after both penetrating keratoplasty (PK)^{17–28} and deep anterior lamellar keratoplasty (DALK).²⁹ It is still not understood if these histological findings are specific to KCN in failed grafts without histologically examining failed grafts from patients without a history of KCN.

In this study, the histological findings from 21 corneas with repeat-PK for KCN, 11 corneas removed for the first time for KCN

and 11 corneas with a repeat-PK due to non-KCN diagnoses were analysed and compared.

METHODS

In this retrospective study, medical records and a histological database of specimens were reviewed from all patients who underwent a primary PK, repeat PK or DALK for KCN between January 2010 and February 2018, at Massachusetts Eye and Ear. This study was approved by the Mass General Brigham institutional review board for retrospective analysis of pathological specimens. In this review, there was a total of 21 consecutive corneal specimens derived from eyes that had previously had a corneal transplant for KCN; these were placed in a group labelled 'failed-PK-KCN'. Multiple reasons for failure included scarring/opacity, graft rejection, oedema, ectasia and infection. The original PK specimens with KCN in 8 of those 21 cases were obtained, which together with three other primary PKs for KCN, were placed into a 'primary KCN' group. For a negative control group, 'failed-PK-non-KCN', corneal transplant tissue from 11 failed corneal grafts that also occurred between 2010 and 2018 from patients whose primary graft had a diagnosis other than KCN were analysed. These included pseudophakic bullous keratopathy (PBK) (5 cases), Fuchs' endothelial dystrophy (2), corneal scarring (1), peripheral ulcerative keratitis (1) and corneal clouding from mucopolysaccharidosis type IV (1). The intent for inclusion of additional groups was to achieve a 2:1:1 ratio corresponding to failed-PK-KCN, primary KCN (positive control) and failed-PK-non-KCN (negative control), respectively. All specimens examined were trephined from the central 7–8 mm of tissue. Graft–host interface tissue was not examined. All surgeries were performed at the surgical department of Massachusetts Eye and Ear by surgeons on the attending staff.

Specimens were collected, de-identified and evaluated by two masked pathologists (PC-B and MH). For each specimen, H&E and Periodic acid–Schiff (PAS) stains were evaluated. A total of three sections (two serial H&E sections and one PAS section) were evaluated for each case and analysed for epithelial basal cell oedema, basal cell mitosis, breaks and/or gaps in Bowman's layer, epithelial basement membrane thickening (on PAS stain),

subepithelial fibrosis, subepithelial neovascularisation and endothelial cell status. For standardisation, an interruption of Bowman's layer that measured two basal cell diameter or less was defined as a 'break', and an interruption of more than two basal cell diameters of Bowman's layer was defined as a 'gap'. The average breaks and/or gaps in Bowman's layer after reviewing 2 H&E and 1 PAS sections were noted for each observer and later tabulated as 1 (for 2 or more breaks/gaps) or 0 (for 1 or fewer breaks/gaps). If there was a discrepancy between the two observers, the cases were re-reviewed in a masked fashion by both pathologists together to achieve a consensus. For this specific approach, the cases of recurrent KCN with discrepancies, negative and positive controls were again included. The stroma was evaluated for oedema, scarring and neovascularisation and the endothelium was assessed according to whether it was intact or attenuated/absent.

Statistical significance was determined using the Fisher's exact test with a conservative Bonferroni two-tailed p value adjusted criterion of $p < 0.017$ ($0.05/3$) as the threshold for statistical significance to reduce the likelihood of Type I error due to three pairwise group comparisons performed. The odds ratio (OR) was calculated using an online calculator (https://www.medcalc.org/calc/odds_ratio.php).

RESULTS

The demographics of the subjects are shown in [table 1](#). The reasons for regrafting in the failed PK-KCN group were stromal opacity (13 cases), corneal oedema (4), infection (1), rejection (2) and ectasia (1).

[Figure 1](#) is a representative image from the failed-PK-KCN group and includes central corneal graft tissue. The tissue was excised 3 years after the original graft due to scarring and oedema. [Figure 1A](#) (H&E) and [figure 1B](#) (PAS) show breaks and gaps in Bowman's layer.

A representative specimen from the primary KCN group is shown in [figure 2](#). This tissue is the native cornea of a patient with KCN displaying breaks and gaps of Bowman's layer seen with the H&E ([figure 2A](#)) and PAS stain ([figure 2B](#)).

[Figure 3](#) demonstrates the findings in a corneal specimen from the failed-PK-non-KCN group. This graft was excised from a patient with a history of Fuchs' endothelial

Table 1 Demographic characteristics of study subjects (mean±SD)

	Failed-PK-KCN	Primary KCN	Failed-PK-non-KCN
n	21	11	11
Age (range)	53.2±17.7 (18–72)	45.8±16.3 (25–69)	62.9±16.9 (35–95)
Laterality % Right Eyes	57%	64%	64%
Penetrating keratoplasty	19	n/a	11
Deep anterior lamellar keratoplasty	2	n/a	0
Years between transplants (range)	11.1±10.8 (0.25–36)	n/a	4.9±6.8 (0.7–25)
DALK, deep anterior lamellar keratoplasty; KCN, keratoconus; PK, penetrating keratoplasty.			

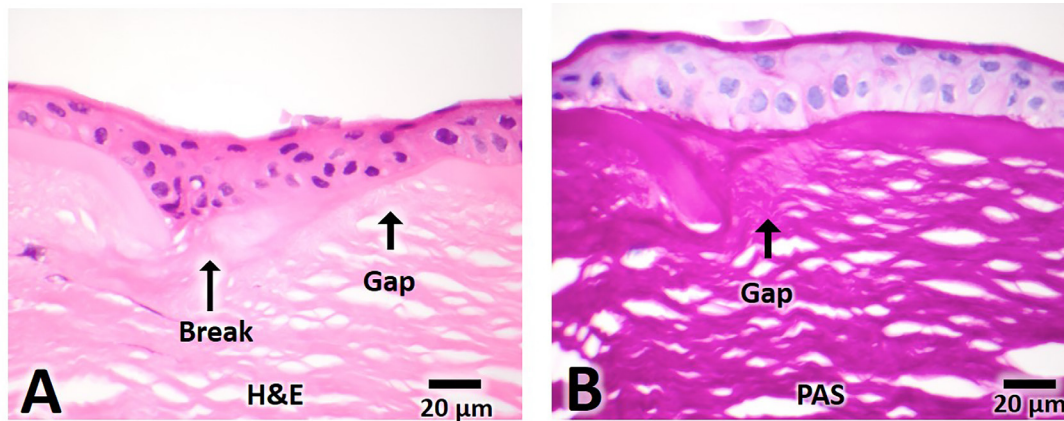


Figure 1 (A) H&E-stained specimen of a failed-PK-KCN case demonstrating a break and a gap of Bowman's layer. (B) Loss of Bowman's layer in a specimen stained with PAS from the same subject. This specimen was excised 3 years after it was originally grafted in a patient with a history of KCN. The corneal graft failed due to scarring and oedema. KCN, keratoconus; PAS, Periodic acid-Schiff.

dystrophy. In [figure 3A](#) (H&E), the epithelium, Bowman's layer and stroma do not show histopathologic alterations. In [figure 3B](#), the PAS stain highlights the epithelial basement membrane (not readily apparent on the H&E stain in [figure 3A](#)).

More than 2 breaks and/or gaps of Bowman's layer in 18/21 (86%) cases were found in the failed-PK-KCN group and in 10/11 (91%) of the primary KCN group, while in only 3/11 (27%) of the cases in the failed-PK-non-KCN group. The proportion of cases with breaks and/or gaps in Bowman's layer in the failed-PK-KCN group was statistically significantly different from the failed-PK-non-KCN group (OR: 16.0, 95% CI 2.63 to 97.2, Fisher's exact test $p=0.0018$). As expected, there was a statistically significant difference between the failed-PK-non-KCN group and primary KCN group (OR: 0.038, 95% CI 0.003 to 0.43, Fisher's exact test $p=0.0075$). The reciprocated OR is 26.7, 95% CI 2.31 to 308.0, indicating a significantly higher prevalence of breaks in the primary KCN group than the failed-PK-non-KCN group, based on a conservative Bonferroni criterion of $p < 0.017$ to

account for multiple group comparisons. There was no statistically significant difference between the failed-PK-KCN and primary KCN groups (OR: 0.6, 95% CI 0.05 to 6.56 (Fisher's exact test $p=0.999$). The reciprocated OR is 1.67, 95% CI 0.15 to 18.2, indicating no difference in the prevalence of breaks during the post-transplant follow-up between grafted patients with history of KCN and negative controls.

Ten out of the 21 (47.6%) grafts in the failed-PK-KCN group had breaks in Bowman's layer within 5 years of transplantation. In contrast, only two out of 11 (18%) grafts in the failed-PK-non-KCN group had breaks in Bowman's layer during the same postoperative period.

There was no statistical significance found between the three groups studied regarding basal cell oedema, basal cell mitosis, basement membrane thickening or subepithelial fibrosis. Stromal oedema, scarring, neovascularisation and endothelial status are shown in [table 2](#).

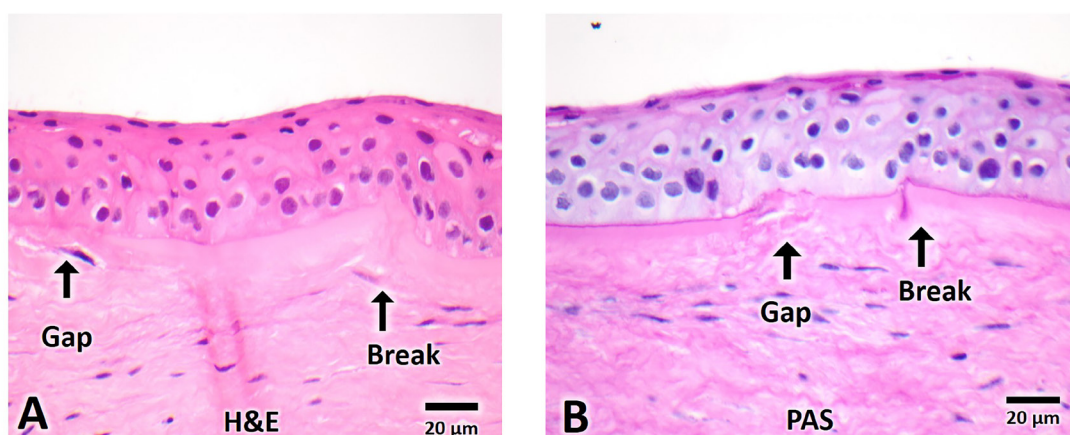


Figure 2 (A) Primary KCN specimen stained with H&E demonstrating a gap and a break in Bowman's layer in patient with the clinical findings of keratoconus. (B) The same specimen stained with PAS. PAS, Periodic acid-Schiff.

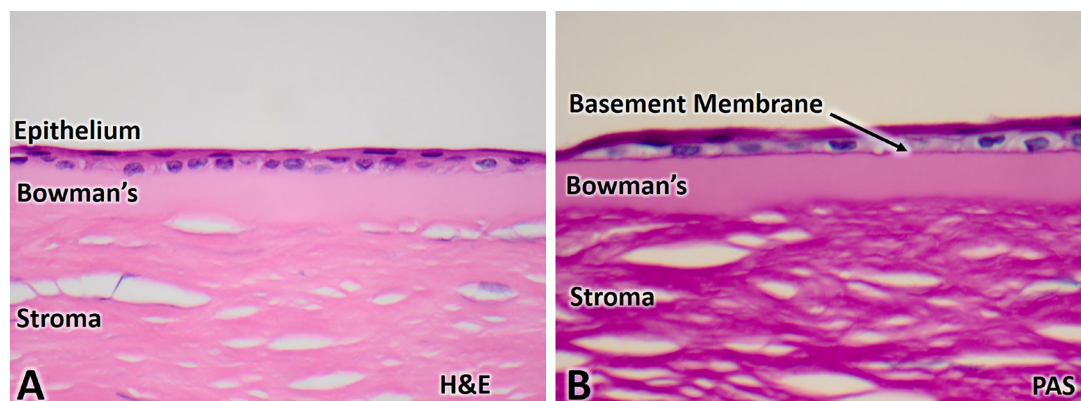


Figure 3 (A) Failed-PK-non-KCN specimen stained with H&E. (B) The same specimen stained with PAS at 60× magnification. Here the basement membrane is a dark purple line between the epithelium and Bowman's membrane. Bowman's membrane is a thick acellular band of the anterior stroma just under the epithelial basement membrane. This is the failed graft from a patient whose primary transplant was for Fuchs' endothelial dystrophy. KCN, keratoconus; PAS, Periodic acid-Schiff; PK, penetrating keratoplasty.

DISCUSSION

In contrast to previous histological studies exploring recurrent KCN,^{17 18 22–25 27 29 30} this study is a masked pathological analysis that compares KCN findings in repeat grafts with those from cases of primary KCN and with those from cases of failed-PK-non-KCN grafts. Breaks and gaps of Bowman's layer are common findings in corneas with KCN.^{11–16} In a histological report of KCN, breaks were reported in 92% of corneas.³¹ Similarly, this study reported breaks in 91% of primary KCN tissues. Moreover, corneas that underwent repeat grafting for KCN were histologically indistinguishable from native corneas with KCN. Breaks and gaps in Bowman's layer were only occasionally present in the failed-PK-non-KCN group.

Histological evidence of recurrence of KCN after corneal transplant was first described in 1980. They observed gaps in Bowman's layer during routine histopathologic evaluation.¹⁷ Since that report, other cases were described in the literature in both traditional PK^{18–23 25–28} and lamellar DALK²⁹ procedures. The presence of the pathological reappearance of KCN after a long latency period has also been described.^{19 20 27} Six patients who had a PK for KCN for at least 10 years underwent a repeat PK, and on unmasked histological analysis, all six corneas had breaks and losses in Bowman's layer consistent with KCN.³⁰

Based on the literature, recurrence of KCN in a graft is considered to be rare and occurs many years after the transplant. In this study, losses and breaks in Bowman's layer were seen as early as 4 months postoperatively where the average years of all the grafts in the study were explanted 9 years post-transplant. Interestingly, almost 50% of the grafts in the failed-PK-KCN group in this study had breaks in Bowman's layer within 5 years of transplantation. This suggests that breaks and gaps in Bowman's layer occur more rapidly than generally thought in grafts with a history of KCN.

There were two specimens in the failed-PK-KCN group that did not have breaks or losses in Bowman's layer. One of the specimens was from a DALK transplant that was 3 years post-transplant and was regrafted because of a vision-limiting opacity. The other specimen was also regrafted because of an opacity and the graft was 10 years post-transplant. Breaks and gaps in Bowman's layer may have been detected if more than three specimens were examined; however, in this study, the histologists were masked and only three specimens were selected for each subject.

In the failed-PK-non-KCN group, three excised grafted tissues also showed breaks and losses in Bowman's layer. Two of the subjects had a history of PBK and one had Fuchs' dystrophy. There was no history of KCN in any

Table 2 Assessment of the stroma and endothelium in specimens from the failed-PK-KCN, primary KCN and failed-PK-non-KCN groups

	Stroma			Endothelium	
	Oedema	Scarring	Neovascularisation	Intact	Attenuated/absent
Failed-PK-KCN (n=21)	19	19	6	4	17
Primary KCN (n=11)	9	9	1	4	7
Failed-PK-non-KCN (n=11)	9	7		1	10

KCN, keratoconus; PK, penetrating keratoplasty.

of the subjects in the failed-PK-non-KCN groups. In the three specimens that demonstrated breaks and gaps in Bowman's layer, a possible but unlikely explanation is that the donor buttons may have had KCN. In PBK, it has been reported that minor disruptions in Bowman's layer have been shown as a result of deposition of fibrocellular material.³² In Fuchs' dystrophy, Bowman's layer changes with confocal microscopy in eight of 17 eyes has been reported.³³ The disruptions in Bowman's layer may result from subepithelial fibrosis due to long-standing oedema from both PBK and Fuchs in the three cases in this study. A limitation of this study was that the age of grafted donor tissue was not reported. The effect that donor age had on the presence of breaks in Bowman's membrane was unable to be determined. Another limitation of this study was that the controls could not be age matched because KCN presented at a younger age than the Fuchs' dystrophy and PBK cases included in this study. However, it has been reported that keratometric changes after PK occur more commonly in eyes with KCN than in eyes with Fuchs' dystrophy,³⁴ and the incidence of the recurrence has been reported to be 6%–11% in eyes with KCN based on clinical presentation, histopathology and keratometric changes.³⁵ Yoshida *et al* defined recurrence of KCN as either acute hydrops or visible whole/inferior graft protrusion and thinning observed clinically. Using these criteria, they identified 36% of 18 grafts within 10 years of PK had recurrent KCN.³⁰ Despite the small sample size, 86% of cases in the failed-PK-KCN group demonstrated histological findings indicative of KCN in the graft itself. Nearly half of these cases demonstrated breaks in Bowman's layer within 5 years of transplantation.

This pathological study only evaluated the central excised tissue, which did not include the graft–host junction. While it has been stated that ectatic changes are a result of thinning of the host tissue near the junction,^{34–38} our results indicate that histopathological findings of KCN are present within the graft itself and occur sooner after surgery than previously reported. It has been noted that the peripheral host cornea becomes thinner following keratoplasty, and that the interface between the thicker donor tissue and thinner host corneal tissue at the graft host junction could contribute to steepening and protrusion of the corneal graft.³⁸ Another limitation of this study is that pathological examination was performed on the central 7–8 mm of excised tissue, which was the donor tissue; the peripheral host tissue was not excised nor was it examined pathologically. Therefore, the relationship between thinning of the peripheral host tissue and the presence of breaks in Bowman's membrane of the donor tissue cannot be established from this study. Future research could determine if there is a correlation between pathological evidence of KCN and keratometric findings.

The mechanism that underlies the possible recurrence of KCN is unclear. It was theorised that keratocytes of the donor tissue were replaced by host keratocytes.¹⁷ These

cells may produce aberrant collagen found in KCN eyes. The global panellists that convened to reach a consensus on the definition, diagnosis and management, including surgical and non-surgical treatments for KCN, did not state that there was a primary pathophysiologic cause of KCN. Instead, they agreed that KCN development included environmental, genetic, biomechanical and biochemical contributions.³⁹ While not common, acute hydrops in grafted patients with recurrent KCN has been reported.^{26 28 30 40} No specimens in the failed-PK-KCN group had hydrops.

It is important to recognise early signs of recurrence of KCN, or ectasia in a grafted patient. In this study, only one subject was regrafted due to ectasia. Ectasia in a PK can be challenging to correct. Corneal steepening from ectasia may induce a myopic shift and increase irregular astigmatism. Contact lens visual rehabilitation is the least invasive treatment for ectasia; it can help improve the vision of these patients. However, some patients undergo PK as an alternative to contact lens correction or are intolerant to contact lenses. Surgical options include compressive sutures, arcuate keratotomy, wedge resection, toric intraocular lens implantation, lamellar keratoplasty, DALK overlay, microkeratome assisted anterior lamellar keratoplasty and repeat PK.⁴¹ Based on the findings of this study, histopathologic signs consistent with recurrence of KCN may be more common and occur earlier than previously thought.

Contributors JC is the guarantor of the article. JC, TD, PL, PC-B and MH planned and designed the study. PC-B, MH, DZ and TD contributed to data collection, data analysis and data interpretation. LJ, PL, TD and JC played leading roles in writing the manuscript. LJ, JC and DZ revised the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The study protocol was approved by the Mass General Brigham institutional review board (Protocol ID: 2019P000259) and adhered to the tenets of the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data is available upon request.

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