



# Contact lens wear and the diabetic corneal epithelium: A happy or disastrous marriage?



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## ABSTRACT

Diabetes mellitus is an epidemic in the US and abroad. With the advent of new contact lens technology, the use of contact lenses as glucose sensors in lieu of the traditional finger stick is quickly becoming realized. This has the potential to rapidly expand the contact lens market into this growing patient population. The independent cellular and physiological effects of contact lens wear and diabetes on the corneal epithelium have been described. However, little evidence exists to date to support whether there is increased risk associated with contact lens wear in diabetes. The focus of this review is to discuss what is known about the cellular effects of contact lenses on the corneal epithelium, the pathophysiological changes in the corneal epithelium that occur in diabetes, and whether an increased risk for corneal epithelial damage and/or infection may negatively impact safety in diabetic contact lens wearers. Available data indicates that there are inherent risks associated with contact lens wear in diabetics. Importantly, eye care practitioners fitting contact lenses in the diabetic patient need to carefully consider the duration of disease, the level of glycemic control, the presence of retinopathy, and the patient's overall health.

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## 1. Introduction

Contact lenses are widely used as an alternative to glasses to correct refractive error, for cosmetic purposes, and as bandage lenses for corneal erosions and painful epithelial defects. The development and implementation of contact lenses for new and exciting indications are rapidly exploding. These indications encompass a wide-spectrum of use, ranging from myopia prevention, drug delivery devices, and biological sensors that monitor intraocular pressure and blood glucose levels.<sup>1–10</sup> With respect to the latter, tear glucose levels have been shown to correlate with blood glucose.<sup>11</sup> Moreover, the implication of tear glucose monitoring using contact lenses offers the advantage of continuous monitoring and is considered to be less invasive than a traditional finger stick.<sup>4</sup>

Concurrent with the introduction of contact lenses into these new markets is the increase in the number of wearers, including children and patients with systemic diseases such as diabetes. Patients with diabetes commonly present to the clinic with damage to the tight epithelial barrier, abnormal wound healing, epithelial fragility, loss of corneal

sensitivity and corneal nerves, and an overall higher risk for bacterial and fungal infections. Despite having a compromised epithelial barrier, little is known about the synergistic effects of contact lens wear on the diabetic corneal epithelium. With the reported increase in Type 1 diabetes mellitus (T1DM) and the massive increase in the numbers of patients with Type 2 diabetes mellitus (T2DM), an understanding of the interactive effects between contact lenses and diabetes on the corneal epithelium is urgently needed.<sup>12–14</sup> Two prior reviews have addressed the ocular complications of contact lens wear in patients with diabetes that commonly present in clinical practice.<sup>15,16</sup> The scope of this review is to re-evaluate the known cellular effects of contact lens wear on the corneal epithelium and the potential impact of contact lens wear on the already abnormal diabetic corneal epithelium.

## 2. The corneal epithelium

The corneal epithelium is a non-keratinized, stratified squamous epithelium that functions to maintain the transparency of the cornea through its innate immuno-protective and tight barrier functions. The cornea is avascularized, a feature required for transparency, and as such the corneal epithelium derives oxygen (155 mm Hg or 21% v/v) from air. During eyelid closure, the available oxygen drops to approximately one third open eye levels. In contrast to this, glucose and other essential nutrients are taken up from the aqueous humor. These molecules are first transported through the leaky barrier of the corneal endothelium and then diffuse anteriorly through the corneal stroma to

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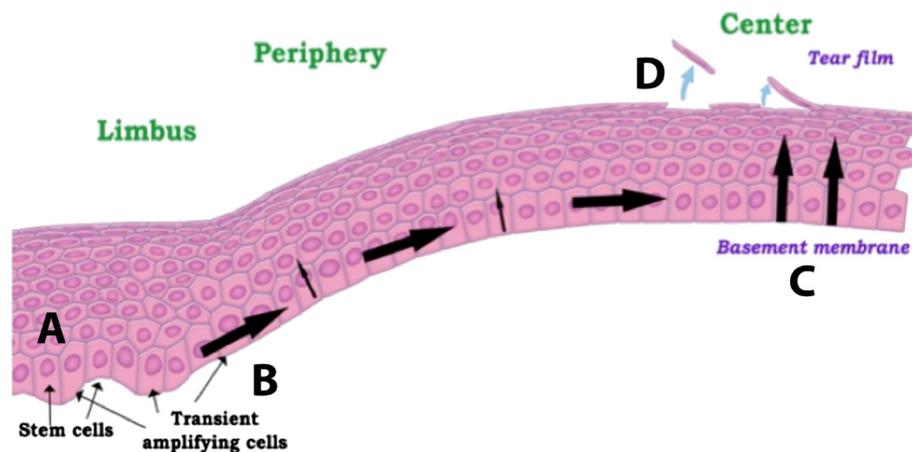
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the epithelium. Excess glucose is converted into glycogen stores, with the highest levels of glycogen residing among the basal epithelial cells to be used during times of stress. Despite the continuous bombardment of insults from shear forces due to blinking, exposure to pathogens, osmolarity changes in diabetes and dry eye, and intermittent hypoxia from overnight eyelid closure during sleep and during low oxygen transmissible contact lens wear, the corneal epithelium is able to maintain a continuous state of self-renewal.

Stem cells that are necessary to replenish the corneal epithelium reside exclusively in the limbal region of cornea.<sup>17–21</sup> Within the basal layer, these cells are protected by the pigmented Palisades of Vogt and nourished by the limbal arcades. The limbal region is unique for the source of corneal stem cells when compared to other tissues. This includes their limbal location, peripheral to the tissue they continuously replenish. Here, limbal stem cells undergo asymmetric cell division, sending one cell on a trek through the peripheral to central cornea, while the other cell is retained. This peripheral migration is associated with a continuous decrease in proliferative capacity. Upon reaching the central cornea, basal epithelial cells undergo their final round of cell division before beginning their vertical ascent towards the corneal surface as paired daughter cells.<sup>17–19</sup> At the corneal surface, post-mitotic, fully differentiated epithelial cells slough or desquamate for clearance by the precorneal tear film (Fig. 1).

### 3. Diabetes and the corneal epithelium

Type 1 and type 2 diabetes are increasing in frequency in young and old patients alike. Diabetes can adversely impact just about every organ system in the body, including the eye. While retinopathy is the most well-known complication of diabetes, the cornea is also adversely affected. In fact, it is estimated that the cornea is adversely affected in up to 70% of all patients.<sup>22</sup> The most studied of the effects on the diabetic corneal epithelium include changes in the composition of the basement membrane, abnormal epithelial cell adhesion, disruption of the epithelial barrier, persistent epithelial defects, and corneal neuropathy.<sup>23–31</sup> These conditions can be visually devastating and unlike retinopathy, are very painful. The molecular mechanisms that underlie corneal complications in diabetes have been reviewed elsewhere (Zhu et al., manuscript in review).<sup>22</sup> Over the past decade, the abundance of reported studies using IVCN to measure diabetes-induced damage to corneal nerves has helped to increase recognition of and the significant unmet need for novel therapies to treat corneal complications, prevent corneal nerve loss, and accelerate corneal epithelial wound healing (Fig. 2).<sup>32–34</sup>



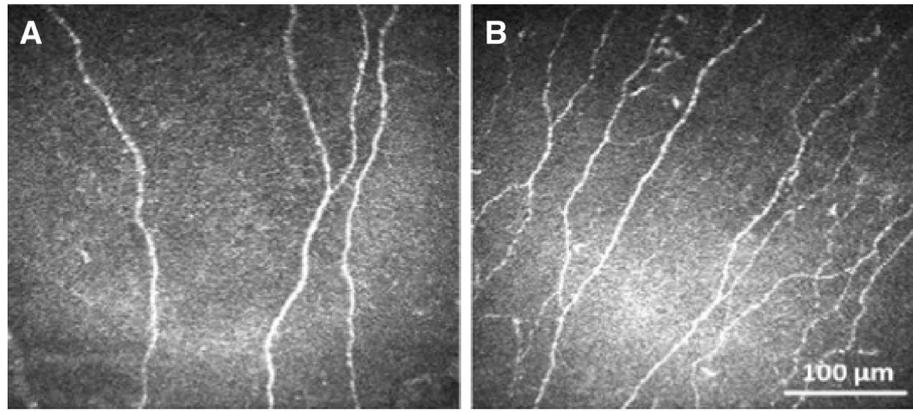
**Fig. 1.** Schematic of corneal epithelial renewal. (A) Stem cells reside in the basal layer of the limbus. (B) Following departure from the limbus, basal epithelial cells become transient amplifying cells and exhibit a high proliferative capacity. (C) Cells continue to migrate to the central cornea, losing proliferative capacity as they go. After the final round of cell division, the paired cells move towards the corneal surface. (D) At the corneal surface, cells are shed or desquamated into the precorneal tear film. Figure taken from Ladage et al. *Contact Lens Ant eye* 2002.

### 4. Corneal epithelial proliferation

In the normal, non-lens wearing rabbit cornea, the proliferation rate is lowest in the limbus, consistent with the localization of slowly dividing basal cells known to reside in this area (Fig. 3). Just adjacent to the limbus, in the peripheral cornea, the proliferation rate is highest and corresponds to the localization of transient amplifying cells.<sup>35,36</sup> This effect is regionally specific, as proliferation is greatest superiorly and decreased inferiorly. This vertical disparity in corneal epithelial proliferation may be explained, in part, by the regional changes in corneal epithelial thickness. Unlike proliferation, corneal epithelial thickness is greatest inferiorly and reduced superiorly (Rashdan et al., manuscript in review). This vertical shift is hypothesized to be a result of eyelid biomechanics. In the central corneal epithelium, the proliferation rate of basal epithelial cells is decreased compared to the peripheral cornea. Studies measuring the proliferation rate in the rabbit limbus have shown increased rates of proliferation in response to rigid gas permeable (RGP) contact lens wear, but not soft contact lens wear. This boost in proliferation is thought to be a direct result of mechanical stimulation from the RGP contact lens that is specific to the rabbit model.<sup>35,37,38</sup> Unlike traditional RGP lens wear in humans, to facilitate lens retention in the rabbit, the contact lens is manufactured with a much larger overall diameter that allows it to cross the limbal border.

In the otherwise healthy cornea, basal epithelial cell proliferation is decreased with all short-term contact lens wear.<sup>37–40</sup> This is partially mediated by hypoxia, as studies have shown significantly decreased numbers of mitotic figures (up to 90%) with very low-oxygen transmissible soft contact lenses.<sup>41</sup> These findings were later confirmed in additional rabbit studies following two days of contact lens wear.<sup>38</sup> Here, the authors demonstrated a greater decrease in proliferation with low oxygen transmissible RGP contact lenses (82% suppression) compared to ultra-high oxygen transmissible RGPs (21% suppression).<sup>38</sup> This finding was also in agreement with a subsequent study that showed an 80% decrease in proliferation following 24 h wear of low-oxygen transmissible RGP contact lenses, whereas, a 37% decrease in proliferation was shown in the ultra-high oxygen transmissible RGP lens group.<sup>37</sup> Not only is basal epithelial cell proliferation decreased in response to hypoxic contact lens wear, but there is also a corresponding reduction in the upward movement of post-mitotic basal epithelial cells towards the surface of the central cornea.<sup>39</sup>

In recent years, there has been little to no work evaluating the effects of contemporary contact lens materials on the proliferation rate of corneal epithelial cells. The most recent study using soft silicone hydrogel contact lenses revealed that the corneal epithelial proliferation rate



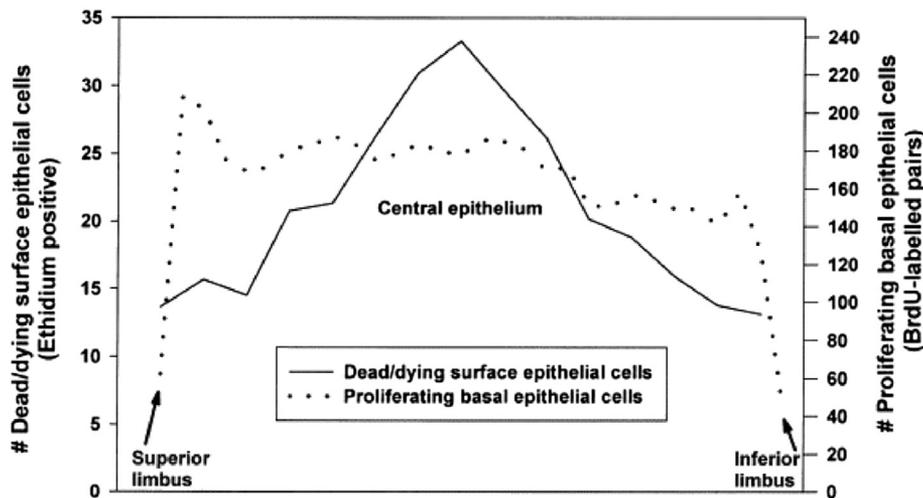
**Fig. 2.** *In vivo* confocal microscopy confirms loss of the human subbasal nerve plexus in diabetes. (A) A representative image of the subbasal nerve plexus in a patient with T2DM. (B) A representative image of the subbasal nerve plexus in a non-diabetic control. Scale bar: 100 µm. Figure taken from Stuard et al. *Invest Ophthalmol Vis Sci* 2018.

decreased following two days of extended wear.<sup>35</sup> Following eight days of extended lens wear, the authors reported an increase in proliferation, which they termed “proliferative recovery”.<sup>35</sup> These data indicate that the attenuation of proliferation of basal epithelial cells in the central cornea following the initiation of contact lens wear undergoes partial adaptation during continued wear. It is unclear whether this proliferative recovery is sustained at this intermediate level, creating a new homeostatic set point in the contact lens wearer, or if it fully returns back to baseline levels. Further studies are needed to fully understand the adaptive effects of the cornea in response to the contact lens.

It is interesting to note however, that this same group also noted changes in the proliferation rate in non-contact lens wearing control eyes when the contralateral eye was fit with either a low or high oxygen transmissible contact lens.<sup>35</sup> A similar finding has been reported for corneal swelling in response to contact lens wear and for growth factor levels in the tear film following wounding.<sup>42,43</sup> Taken together, these data suggest that there is a central control mechanism regulating communication between eyes, in which perturbation to one eye triggers a similar response, albeit lower in magnitude, in the contralateral eye.

It is unknown whether the stagnation in corneal epithelial renewal that occurs in response to contact lens wear is a contributor to infection. Since the corneal epithelium functions as an innate barrier, it would be

intuitive to speculate that any disruption to this barrier may lower host defenses. In the diabetic corneal epithelium, it is well established that there is functional impairment of the tight barrier and reduced adhesion of epithelial cells to the basal lamina. Abnormalities in epithelial cell proliferation have also been reported however, the data is somewhat conflicting.<sup>44,45</sup> Fujita and colleagues cultured corneal epithelial cells in the presence of elevated extracellular glucose and reported significant decreases in both cell number and tritiated thymidine incorporation, indicating a reduction in proliferation.<sup>44</sup> In contrast to this, McDermott et al. demonstrated an increase in proliferation in high glucose cultures.<sup>45</sup> Using Simian virus-40 (SV-40) transformed corneal epithelial cells, they found an increase in extracellular glucose from 5 mM to 17.5 mM increased proliferation by 44%. Further increases in glucose concentration failed to significantly alter proliferation. Our own unpublished observations using primary cultured human corneal epithelial cells from diabetic cadaveric donors have yielded mixed results on the effects of diabetes on epithelial proliferation. Growth of these cells in standard keratinocyte culture media containing 6 mM glucose ranges from a slight reduction in growth to almost completely arrested proliferation. It is important to note that these are cells that have been subject to long standing diabetes *in vivo* and not an acute exposure to elevated glucose that is commonly tested in cell culture models. More work is



**Fig. 3.** Distribution of basal epithelial cell proliferation and surface cell shedding in the rabbit cornea. 5-bromo-2'-deoxyuridine (BrdU) labeling of mitotic cells across the limbal and corneal epithelium (dotted line) shows an increase in proliferation in the superior limbus. Calcein-ethidium live/dead staining showing a central peak in non-viable cells in the surface epithelium (solid line).

Figure taken from Ladage et al., *Contact Lens Ant Eye* 2002.

needed to fully define the effects of diabetes, in addition to glucose, that impact normal proliferation and growth of the corneal epithelium.

### 5. Apoptosis and surface epithelial cell desquamation

Previous reports have shown that in the normal, non-lens wearing eye, corneal epithelial cells are sloughed into the precorneal tear film *via* apoptosis, a regulated form of cell death.<sup>46</sup> This is mediated in part, by loss of the nuclear localized anti-apoptotic protein, B-cell lymphoma-2 (Bcl2).<sup>47–49</sup> When examining the non-lens wearing cornea, the lowest numbers of nonviable cells were found in the limbus, while there were a greater number of nonviable cells in the central cornea (Fig. 3). While limited research on the mechanism(s) that regulate apoptotic shedding in the corneal epithelium is available, multiple reports using human and animal models have confirmed that there is a reduction in apoptotic shedding during contact lens wear.<sup>47,50–54</sup> O'Leary was the first to show that there was a decreased number of epithelial cells irrigated from the human corneal surface following contact lens wear.<sup>55</sup> In his study, O'Leary compared cells that were presumably exfoliated from the corneal surface following soft or RGP contact lens wear compared to controls. In doing so, he found that both soft and RGP lenses disrupted normal desquamation. This work was later confirmed in multiple, prospective human clinical trials.<sup>52–54</sup> These studies further showed that this decrease in apoptotic desquamation rate was greatest following 1 month of lens wear and similar to proliferation, showed a partial adaptive recovery after one year.<sup>53,54,56</sup> Moreover, desquamation rate was not mediated by the duration of extended wear, since there were no detectable differences between 6 and 30 day wearing regimens.<sup>53,54</sup>

It has also been proposed that during contact lens wear the contact lens may act as a barrier to protect the corneal epithelium from the mechanical shearing forces that result during blinking and that these forces may provide the trigger that drives desquamation of terminally differentiated corneal epithelial cells from the surface of the eye. This theory is not supported by work by Ren and colleagues using nitrogen goggles that showed an inhibition of desquamation during hypoxia in the absence of a contact lens.<sup>57</sup> It is more likely that both hypoxia and shear forces contribute to altered desquamation in response to contact lens wear. The exact mechanism(s) still remain ill defined.

There is a paucity of evidence examining the effects of diabetes on the regulation of apoptotic desquamation from the surface corneal epithelium. In dry eye, epithelial turnover increases and this is associated with a corresponding increase in non-viable surface epithelial cells.<sup>58</sup> One could speculate that in diabetes, where there is an increase in dry eye, cellular desquamation is escalated.<sup>59–66</sup> In a diabetic rat model, terminal deoxynucleotidyl transferase dUTP nick end (TUNEL) labeling was used to measure the number of apoptotic cells in the corneal epithelium.<sup>67</sup> Importantly, the authors found a five-fold increase in apoptotic cells compared to the non-diabetic control. Apoptosis in this model was mediated by cleavage of caspase 3. Similar findings have been reported in cultured corneal epithelial cells.<sup>68</sup> Specifically, reports have shown an increase in inflammatory mediators and apoptosis in response to an increase in extracellular glucose.<sup>68</sup> Likewise, the accumulation of advanced glycation end products has also been shown to induce apoptosis in corneal epithelial cells.<sup>69</sup> The increase in apoptotic surface shedding of surface corneal epithelial cells may be somewhat protective in the diabetic eye, at least for invasive bacterial strains that undergo lipid-raft mediated internalization.<sup>70</sup> However, as described above, this mechanism is blunted during contact lens wear.

### 6. Corneal epithelial thickness and epithelial cell size

Clinical studies using *in vivo* confocal microscopy through focusing have shown that extended wear, but not daily wear, of contact lenses results in thinning of the corneal epithelium.<sup>54,56,71–73</sup> This appears to be mediated partly by hypoxia as low oxygen permeable lenses result

in more significant corneal epithelial thinning.<sup>54,72,73</sup> Likewise, wear of RGP lenses have the greatest effect on epithelial thickness, likely due to the mechanical pressure of the lens on the cornea.<sup>53</sup> With soft lenses, duration of wear does not appear to be a significant contributor to the corneal epithelial thinning seen in extended contact lens wear,<sup>53,73</sup> as there was no significant difference between 6 days *versus* 30 days of extended wear.<sup>53,54</sup> Similar to proliferation rates, there is a partial adaptive recovery after the first month of extended wear, resulting in partial restoration of epithelial thickness.<sup>53</sup> After cessation of lens wear, thickness of the epithelium fully recovers over time. This was demonstrated by Holden and colleagues who found that after extended wear, it took 33 days for the central epithelial thickness to fully return to baseline levels.<sup>71</sup>

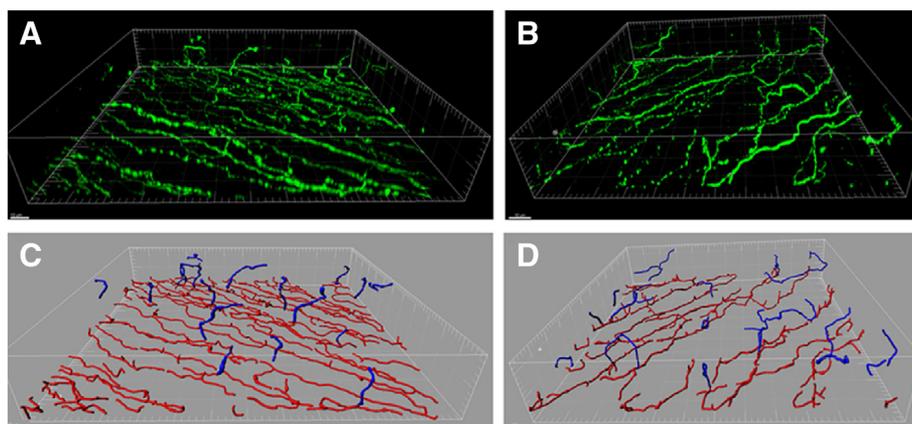
The reduction in epithelial proliferation and desquamation combined with epithelial thinning is thought to create a “stagnant” epithelium. Consistent with this theory, there is an increase in surface epithelial cell size in response to contact lens wear. Tsubota and Yamada were the first to demonstrate an increased epithelial cell size using specular microscopy.<sup>74</sup> In that study they found that an increase in surface epithelial cell size was exclusively associated with extended wear of soft contact lenses.<sup>74</sup> In a subsequent report evaluating contact lens wearers over a six month period, Tsubota et al. also demonstrated that surface epithelial cell size increased linearly with the duration of extended wear.<sup>75</sup>

Increased cell size from contact lens wear has since been confirmed using *in vivo* confocal microscopy.<sup>52,53,76</sup> In a series of 12-month prospective clinical studies, all overnight or extended contact lens wearers showed significant increases in surface epithelial cell size.<sup>54,77–79</sup> This effect was greatest with rigid lenses due to the mechanical effect of the lens on the corneal surface.<sup>52,53,79</sup> In contrast to prior reports however, the area of surface epithelial cells calculated from *in vivo* confocal microscopy (IVCM) images failed to detect a difference in cell size regardless of whether lenses were worn for 6 or 30 days. Rather than a linear increase in cell size for longer durations of wear, they also found an early rapid increase that tapered-off over time. No long-term adaptation was observed for surface cell size in this yearlong trial.<sup>53</sup> Compared to the work by Tsubota et al., these latter two findings yielded contradictory results regarding the effect of RGP lenses and the linear relationship between duration of lens wear and surface epithelial cell size. The impact of daily lens wear on surface corneal epithelial cell size is also conflicting. While Tsubota did not detect a difference in surface area between daily lens wearers compared to controls, Ladage demonstrated a significant increase in surface epithelial cell size during 4 weeks of daily wear.<sup>52,74</sup>

Similar to contact lens wear, at the tissue level, central corneal epithelial thinning is frequently reported in patients with diabetes. Unlike corneal epithelial thinning during contact lens wear that is thought to be driven by hypoxia and/or lens biomechanics, corneal epithelial thinning in diabetes is driven by the loss of corneal sensory nerves. Rosenberg et al. were the first to use IVCM to document corneal epithelial thinning in diabetes.<sup>80</sup> In agreement with this work, animal studies in our laboratory have also confirmed that the cornea thins in severe diabetes and is associated with damage to the subbasal nerve plexus (Fig. 4).<sup>81</sup> It should be noted that corneal epithelial thinning has not been demonstrated in all animal models of diabetes.<sup>82,83</sup> This difference could be due in part to the severity of the disease, whether insulin was administered, and the method in which epithelial thickness was measured.

### 7. Stem cells

Stem cells reside in the basal layer of the limbus, the area located at the intersection of the corneoscleral junction.<sup>20,21</sup> Stem cells are necessary for normal homeostasis of the epithelium and function to restore the epithelium following wounding. Clinically, the loss of stem cells is diagnosed as limbal stem cell deficiency (LSCD). There are multiple



**Fig. 4.** Epithelial thinning is associated with loss of the subbasal nerve plexus in a Type 1 streptozotocin diabetic mouse model. (A) Three-dimensional surface rendering of the subbasal nerve plexus and associated terminal epithelial nerves in a control mouse.  $\beta$ -Tubulin III staining in green. (B) Three-dimensional surface rendering of a Type 1 diabetic mouse. Scale bar: 10  $\mu$ m. (C–D) Nerve modeling and segmentation using IMARIS Filament. Representative images of the subbasal nerve plexus is shown in red, terminal epithelial nerves in blue (C, normal; D diabetic). Scale bar: 10  $\mu$ m. Loss of the subbasal nerve plexus in (D) was associated with significant thinning of the corneal epithelium after 12 weeks of diabetes,  $34.0 \mu\text{m} \pm 3.0 \mu\text{m}$  (diabetes) compared to  $38.6 \mu\text{m} \pm 3.8 \mu\text{m}$  (control). Figure taken from Cai et al. *Am J Pathol* 2014.

known etiologies for limbal stem cell deficiency, consisting of congenital and acquired causes and can affect one, and more rarely, both eyes. These include ectodermal dysplasia, aniridia, chemical or thermal injuries, Stevens-Johnson syndrome, and iatrogenic cases (secondary to surgery or medications).<sup>84–86</sup> To date, LSCD is still regarded as a major complication of contact lens wear.

Clinically, loss of limbal stem cells results in conjunctivalization of the cornea with resultant corneal opacification.<sup>84–86</sup> LSCD can produce signs and symptoms of decreased vision, photophobia, pain, tearing, redness, and irritation. In some wearers, particularly those in the early stages of damage, LSCD is asymptomatic.<sup>86–88</sup> In fact, a retrospective review estimated that contact lens-induced LSCD was asymptomatic in more than 70% of patients.<sup>85</sup> Almost all reported cases are due to many years of soft contact lens wear and are associated with significant inflammation.<sup>85,88–90</sup> The pathogenesis of contact lens-induced LSCD is thought to be multifactorial involving mechanical trauma from the lens,<sup>85,91</sup> toxicity from contact lens solutions and their preservatives,<sup>92</sup> chronic hypoxia,<sup>94</sup> and disruption of the pre-ocular tear film.<sup>95</sup> Contact lens induced hypoxia has been shown to be greatest in the superior cornea.<sup>96,97</sup> This, combined with the mechanical irritation in the superior limbus from the eyelid/contact lens interaction, may explain the increased prevalence of contact lens-induced LSCD in this region.<sup>98</sup>

Very little is known regarding the impact of diabetes on limbal stem cells. In diabetic corneal tissue, staining at the limbus for the membrane transporter protein, ATP binding cassette subfamily G member 2 (ABCG2), and the transcription factor  $\Delta$ Np63 $\alpha$  revealed a large decrease in both markers.  $\Delta$ Np63 $\alpha$ , once considered a putative stem cell marker in the cornea, is now well recognized as a known marker of proliferative capacity.<sup>99</sup> Thus, the blunted expression of  $\Delta$ Np63 $\alpha$  seen in the diabetic cornea is consistent with the delay in corneal re-epithelialization that is frequently reported in diabetes. In support of this, expression of  $\Delta$ Np63 $\alpha$  is also significantly downregulated in the rabbit contact lens model in response to hypoxic contact lens wear, which is known to attenuate basal epithelial cell proliferation.<sup>100</sup>

Similarly, immunostaining for the cytokeratin marker K17 was almost completely abolished in diabetic corneal tissue, along with reduced expression of cytokeratins K15 and K19. Likewise, integrin  $\beta_1$ , laminin and fibronectin were also reduced, suggesting potential mechanisms that may contribute to altered epithelial cell adhesion.<sup>101</sup> More recently, work by this same group has shown that the miRNA profile in the diabetic limbus differs substantially from the miRNA profile in healthy, non-diabetic limbal controls.<sup>102</sup> While further in depth studies are needed to understand the effects of diabetes on this delicate limbal compartment, the molecular changes identified to date provide some

mechanistic insight into the cellular changes that have been well described. Further, understanding the effects of continuous low-grade inflammation that arises secondary to altered aqueous tear secretion in diabetes-related dry eye, coupled with the physical pressure of a contact lens on the eye, illustrates a critical unmet need that warrants additional study.

## 8. Corneal nerves

The cornea is the most innervated tissue in the body, with approximately 7000 nociceptors/ $\text{mm}^2$  within the central cornea alone.<sup>103</sup> These sensory nerves are essential to drive tear production and maintain the blink reflex. In relation to the corneal epithelium, trophic factors released by corneal nerves are necessary for maintaining corneal epithelial homeostasis. In support of this view, Beuerman and colleagues in the early 1980's demonstrated that denervation of the trigeminal nerve not only disrupted corneal epithelial integrity but also adversely affected corneal wound healing.<sup>104</sup>

The effects of contact lens wear on the subbasal nerve plexus are not well described. Early studies showed that contact lens wear triggers a reduction in corneal sensitivity; however, this decrease was primarily driven by lens-induced hypoxia.<sup>105</sup> Murphy and colleagues also demonstrated a reduction in corneal sensitivity during contact lens wear.<sup>106</sup> In their study, they found that loss of corneal sensitivity was independent of lens type (soft versus rigid), did not vary with duration of contact lens wear, and occurred during the first few months of wear.<sup>106</sup> In contrast to corneal sensitivity, more recent work using *in vivo* confocal microscopy to visualize the subbasal nerve plexus have failed to detect a difference in corneal nerve morphology in contact lens wearers compared to non-wearers.<sup>107</sup> Similarly, Oliveira-Soto and Efron were unable to detect a quantitative loss of the subbasal nerve plexus following contact lens wear. Instead, they observed qualitative changes in the morphology of the subbasal nerves.<sup>108</sup> This difference was attributed to corneal edema in response to overnight lens wear.

It is well established that damage to the subbasal nerve plexus occurs in diabetes. The literature is extensive and has been reviewed elsewhere.<sup>109–113</sup> Loss of the subbasal nerve plexus in diabetes is thought to significantly impede corneal epithelial homeostasis. Clinically, this results in a loss of barrier function, corneal erosions, and persistent epithelial defects.<sup>27,114,115</sup> Dry eye is also not uncommon in diabetics, stemming from damage to sensory nerves and the attenuation of lacrimation and blink reflexes.<sup>116</sup> Moreover, the efficacy of treatment for dry eye is mediated in part by the density of the subbasal nerve plexus.<sup>117</sup> This further highlights the underlying need for a healthy

subbasal nerve plexus to maintain the health of the corneal epithelium. The interplay between contact lens wear, subbasal nerve loss, and corneal epithelial changes has not been well investigated. Even with the use of silicone hydrogel lens materials, which eliminate the hypoxia-driven loss in corneal sensitivity during contact lens wear, it is unknown whether diabetes-induced corneal damage may precipitate and predispose the wearer to contact lens-related corneal infections.

## 9. Infection

Hallmark studies in the late eighties established the annualized incidence of corneal infection with contact lens wear.<sup>118,119</sup> Since that time, lens materials have continued to evolve. The introduction of silicone hydrogel contact lenses into the mainstream population led to a major improvement in corneal physiology.<sup>120,121</sup> In terms of extended wear, there was a shift in the risk for corneal infection.<sup>122</sup> Specifically, it was determined that duration of lens wear was no longer a risk factor for corneal infection. In fact, 30 day extended wear held the same risk as 6 night extended wear. Despite this initial progress, follow up epidemiological studies found that the overall annualized incidence of contact lens-related infectious keratitis in daily and extended wear remained relatively unchanged.<sup>123</sup> Coupled with data reported in earlier studies that showed that exposure of the surface corneal epithelium to a hypoxic environment disrupted epithelial desquamation but did not increase bacterial binding to shed cells, confirms that the actual presence of the contact lens on the eye, regardless of oxygen transmission, is the key requirement that underlies the pathophysiology of contact lens-related infection.<sup>57,121</sup>

In diabetes, the level of complexity increases. In general, published data indicates that individuals with T2DM are more prone to infections.<sup>124</sup> This includes infections with bacteria, fungus and yeast. Fungal and yeast infections have also been reported to be more frequent in diabetics and are a major cause of disease morbidity.<sup>125</sup> This is thought to be due in part to altered immunity in this patient group. It has also been postulated that in poorly controlled subjects, increasing glucose levels in tears, saliva, urine, skin and blood may serve as a food source for these pathogens.<sup>126</sup> In agreement with this, a recent large-scale retrospective study in the UK found that non-eye microbial infections were the most common in subjects with poor glycemic control.<sup>124</sup>

The relationship between adequate glycemic control and infection risk is somewhat controversial, particularly in relation to the eye. While not focused specifically on diabetes, Keay, Edwards, and Stapleton identified poor systemic health as a risk factor for microbial keratitis.<sup>127</sup> In his landmark epidemiology study published in 1989, Schein was the first to identify diabetes as the only systemic disease that was associated with an increased risk for contact lens-related microbial keratitis.<sup>128</sup> Eichenbaum also reported on four cases of severe corneal ulcers in aphakic contact lens wearers.<sup>129</sup> In that study, three of the four patients reported had a positive medical history for diabetes with no evidence of retinopathy or poor glycemic control.

Somewhat conflicting with Schein, Ansari and colleagues found that in the case of eye infections, subjects with diabetes were more likely to present with conjunctivitis, but there was no increased incidence of keratitis in diabetics and the severity of infection was not related to glycemic control.<sup>130</sup> Wang et al. also examined the incidence of keratitis in T2DM compared to non-diabetics.<sup>131</sup> Unlike Ansari's report, Wang concluded that diabetics were more prone to bacterial keratitis but there was no difference between diabetics and controls for fungal or amoebic cases. Dan et al. also examined eyes with diabetes compared to controls and reported that diabetes was in fact an independent risk factor for severe fungal keratitis.<sup>132</sup> Moreover, in diabetics with severe fungal infections that underwent a penetrating keratoplasty to restore vision, there was a significantly increased incidence of delayed re-epithelialization. The duration of T2DM was a major factor that impacted restoration of the corneal epithelial surface.

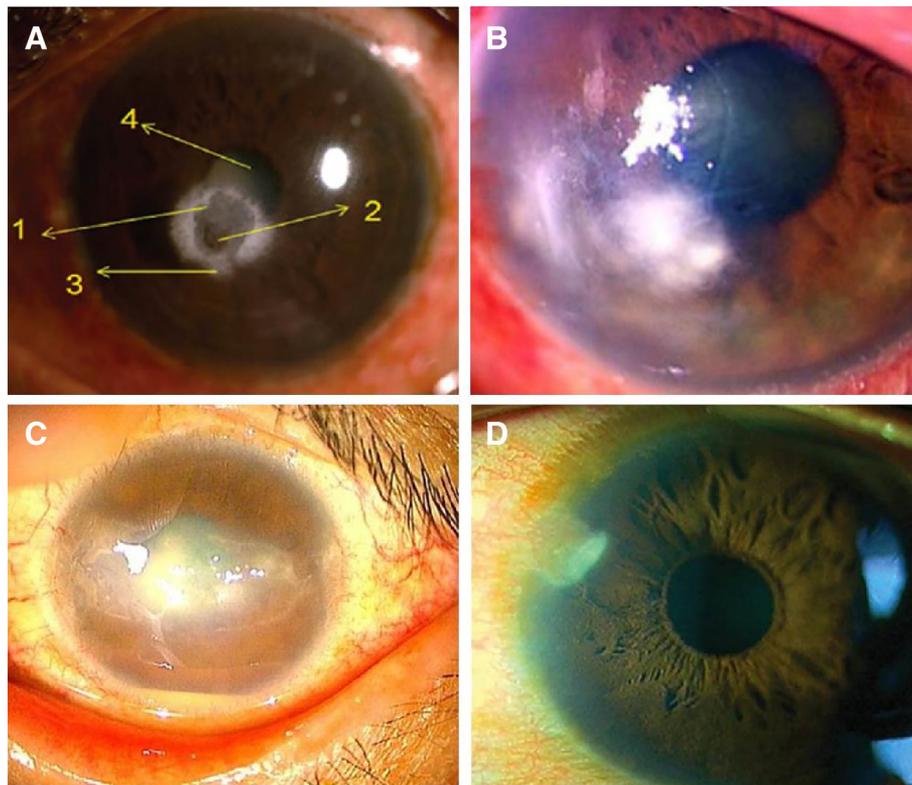
One potential explanation for the increased risk of microbial keratitis in diabetics stems from the shift in the conjunctival flora. Reports by multiple independent groups confirm that swabs taken from the inferior palpebral conjunctiva in diabetics have a higher rate of positive cultures compared to non-diabetics.<sup>133–136</sup> These studies also indicate that the presence of diabetic retinopathy is associated with a higher rate of positive cultures. There is some variability however, regarding the composition of the conjunctiva flora in diabetics. Most studies have reported an increase in gram-positive cultures, principally *Staphylococcus* spp. in diabetics. This increase is likely due to the greater number of diabetics compared to non-diabetics that present to the clinic with blepharitis.<sup>15</sup> One report however, found an increase in gram-negative bacteria in the diabetic group compared to controls.<sup>137</sup> It was postulated that this may be due to regional or seasonal differences. Further studies are needed to investigate these findings.

Rare cases of microbial keratitis have also been reported in diabetics (Fig. 5). *Prototheca wickerhamii* is an alga that abounds in the environment but is rarely associated with disease. In the eye, keratitis due to *P. wickerhamii* has only been reported in individuals with severe immune deficiencies or following intraocular surgery. In their recent paper, Tobimatsu and colleagues reported a case of a 46-year old diabetic male who developed *P. wickerhamii* keratitis following an eye injury (Fig. 5A).<sup>138</sup> Similarly, a recent case report identified an 82-year old man with diabetes who presented with a severe fungal keratitis due to *Rousoella solani* (Fig. 5B).<sup>139</sup> This was the first known case of a fungal keratitis due to this pathogen. Of high relevance to this case, the patient had no prior history of trauma with any type of soil or vegetative matter.

Keratitis secondary to *Corynebacterium propinquum* has also been reported in a diabetic patient who was undergoing treatment with a bandage contact lens (Fig. 5C).<sup>140</sup> The subject, a 44-year old female with T1DM, nephropathy, and bilateral proliferative diabetic retinopathy, initially presented to the clinic with a persistent epithelial defect. While *C. propinquum* is commonly isolated from the respiratory tract, other species of *Corynebacterium* comprise part of the conjunctival flora. In this case, the organism was cultured from the cornea and appropriate antimicrobial therapy led to complete resolution of the infection. Not surprisingly, re-epithelialization was significantly delayed and took several months to fully heal. In another case, a 41-year old male with a history of diabetes and poor glycemic control presented to the clinic with eye pain, redness, tearing, and photophobia (Fig. 5D). Cultures confirmed a diagnosis of microbial keratitis secondary to the gram-negative bacteria *Stenotrophomonas maltophilia*.<sup>141</sup> Importantly, the patient denied any history of recent ocular trauma, surgery, or contact lens wear and no other comorbid disease was present. This infection was considered spontaneous and secondary to his non-controlled diabetes. While these case studies are in no way a conclusive list, they do highlight the increased risk for microbial keratitis in patients with diabetes and an increased risk for pathogens not commonly reported clinically.

## 10. Tear glucose monitoring

With an established relationship between tear and serum glucose and the reported findings that tear glucose levels are frequently elevated approximately 5 fold in diabetics compared to non-diabetic patients, the use of tear glucose-based contact lenses have received significant attention in recent years.<sup>142</sup> Multiple designs and monitoring paradigms for these novel lenses are in development and have been described elsewhere.<sup>4</sup> Many of these designs include embedding a glucose sensor into either a conventional hydrogel or silicone hydrogel lens material, both of which are approved by the Food and Drug Administration (FDA) for daily contact lens wear. It has also been hypothesized that not only will these lenses allow for continuous tear glucose monitoring throughout the day, but they may be worn in an extended wear modality to monitor for glucose changes during sleep. Given the well-established increased infection risk with overnight or extended contact



**Fig. 5.** Corneal ulcers reported in diabetic patients. (A) Corneal ulcer caused by *Prototheca wickerhamii*. Numbers as described as detailed in the original case report. 1: central ulcer; 2: region of corneal thinning; 3: large infiltrate surrounding the ulcer; 4: lenticular changes. Image taken from Narayanan et al. *Indian J Ophthalmol* 2018. (B) Corneal ulcer caused by *Roussoella solani*. Image taken from Mochizuki et al. *J Infect Chemo* 2017. (C) Corneal ulcer caused by *Corynebacterium propinquum*. Image taken from Todokoro et al. *J Clin Microbiol* 2015. (D) Corneal ulcer caused by *Stenotrophomonas maltophilia*. Image taken from Holifield et al. *Eye Contact Lens* 2011.

lens wear, the use of lens-based glucose sensors for continuous overnight wear greatly heightens the potential risk associated with these lenses.<sup>118,143,144</sup> Infection risk aside, there are other biological considerations that may limit the use of contact lenses as glucose monitors. These include diurnal and day to day variations in tear glucose levels in addition to the effects of reflexive tear stimulation and dry eye.<sup>145</sup> The need for calibration of these monitoring devices and their biocompatibility with contact lens care systems and cleaning regimens (such as digital rubbing to clean the lens) have not yet been reported.

## 11. Conclusions

Only a handful of studies have examined the potential for adverse ocular events in contact lens wearers that are diabetic.<sup>146–148</sup> More large scale, prospective studies to evaluate the pathobiology of the diabetic corneal epithelium under the contact lens are needed to establish an actual level of safety. Many of the cell culture studies that function to tease out the molecular dysregulation that occurs in diabetes are performed in the presence of elevated extracellular glucose. Maintaining optimal glycemic control is necessary for preventing diabetic complications in Type 1 disease.<sup>149,150</sup> Unfortunately, while glycemic control is also important in Type 2 disease, it is not the only factor that predisposes this patient population to the development of complications, including those involving the eye. Other key factors include inflammation, oxidative stress, metabolic alterations, and epigenetic modifications.<sup>151–154</sup>

It is well established in the literature that diabetics do carry an inherent increased risk for infection. Likewise, microbial keratitis secondary to the presence of rare organisms has been reported. The independent effects of contact lenses and diabetes on the corneal epithelium have been reasonably well characterized. However, the scope and magnitude

of these changes vary with lens material and the severity of disease. It remains unknown how epithelial homeostasis is disrupted during contact lens wear in the presence of systemic disease. Given the continued rise in the prevalence of diabetes in the US and abroad and the potential for contact lens wear to explode within this patient population, it is imperative that the clinician pay particular attention to the duration of diabetes, the level of glycemic control, the presence of retinopathy, and the patient's overall health status when making the decision whether to fit contact lenses. While not discussed in this review, the existing level of corneal sensitivity should also be documented. This is especially important when treating diabetic patients with epithelial abnormalities or abrasions arising secondary to contact lens wear.

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