

Diabetes *Impacts on the Cornea and Anterior* *Segment*

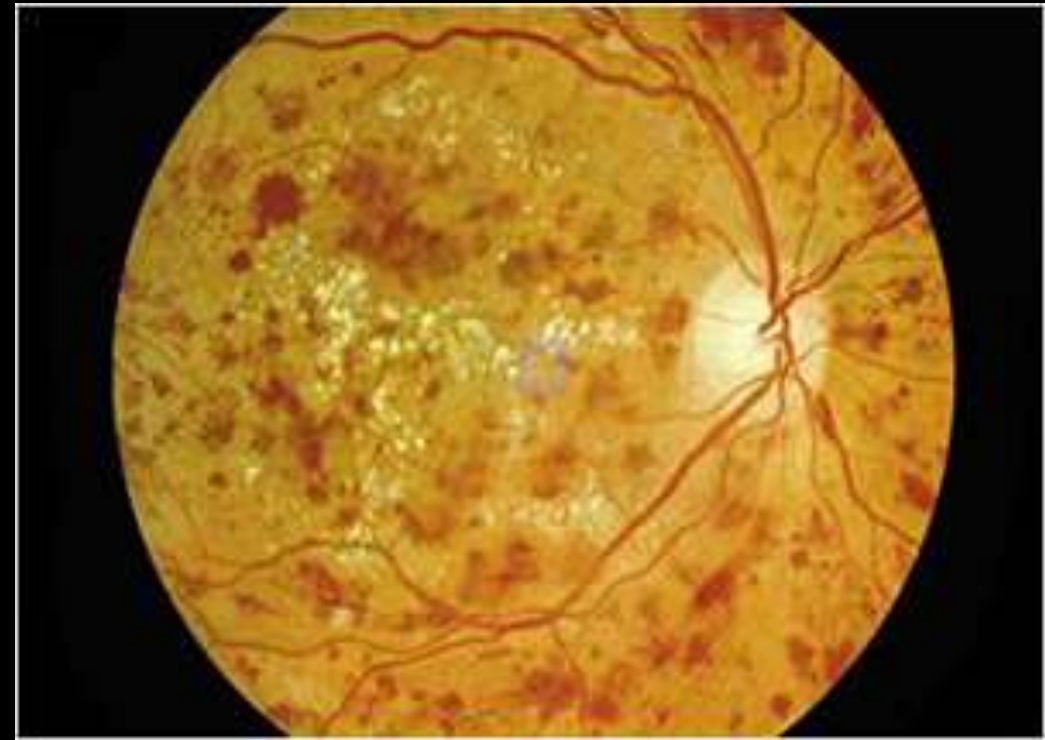
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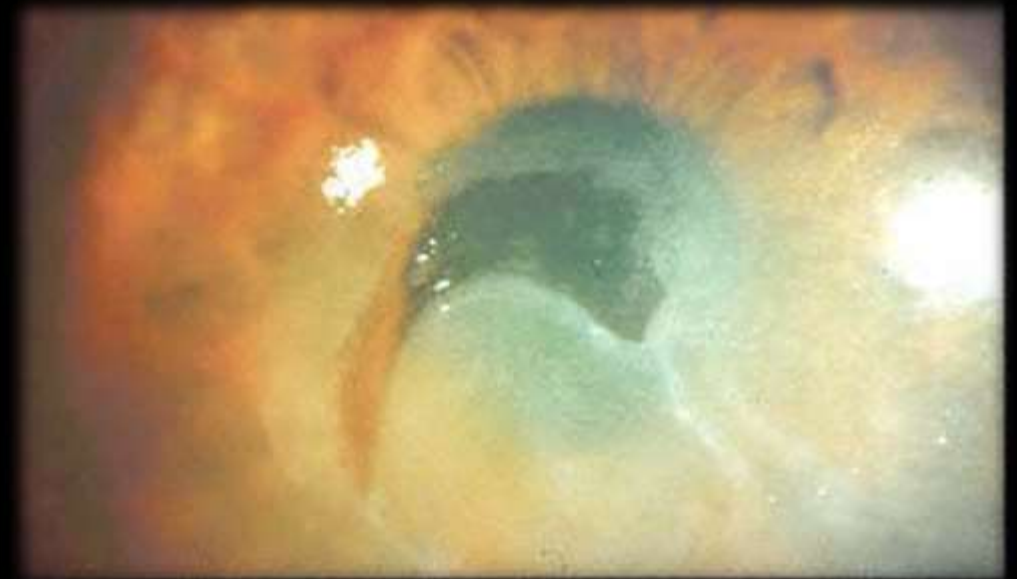
OCULAR DIABETES


- *Ocular diabetes* has a great morbidity in the world.
- *Diabetic retinopathy (DR)* is a well-known vascular entity, and it may be the most frequent cause of visual loss in these patients.
- Besides the retinal involvement, diabetes mellitus (DM) may affect the *anterior ocular segment, especially the ocular surface.*



ANTERIOR SEGMENT IMPACTS

- **Altered corneal sensory nerves and neurotrophic defects** are often found in these patients. Likewise, an **associated dry eye** can also be present.
- **Cataracts** are common in the diabetic population. The risk of diabetic macular edema following phacoemulsification surgery is increased.
- **Intravitreal anti-VEGF** agents and corticosteroids are used frequently. Nevertheless, these repetitive therapies **could be toxic for the corneal endothelium**.



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- *Good glycemic control* is essential *to avoid* the appearance of pathological alterations in the previously mentioned territories.
 - The *ocular surface* serves to help correct diagnosis and follow-up of the diabetic patients.
 - The measurement of *glucose concentration in the tear film* is a *noninvasive* test which can show blood glucose changes throughout the day without needing punctures or blood tests.

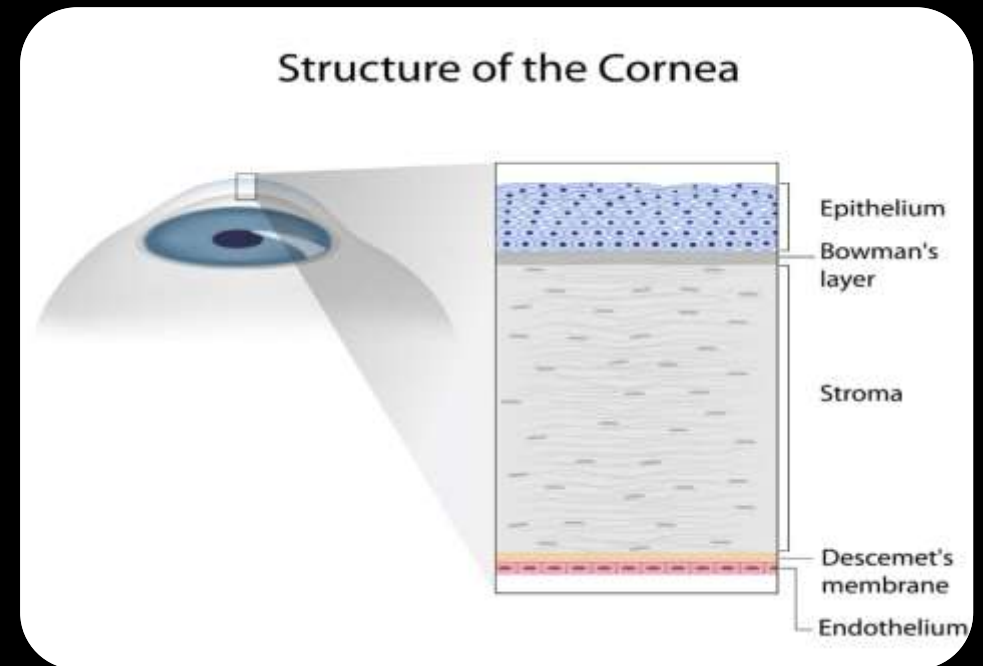
DIABETIC CORNEAL DISEASE

- *Diabetic corneal disease* is a significant clinical problem affecting over a *half* of diabetic population.
- However, it is not receiving proper attention from physicians and remains *underdiagnosed* and *underestimated*.
- Clinical manifestations mainly concern *epithelial problems, neuropathy* (loss of corneal sensation and possibility of developing *neurotrophic ulcers*), and *tear film alteration*.

GENERAL MANIFESTATIONS OF DIABETES IN THE CORNEA

Clinically observed *corneal diabetic alterations* include:

- ✓ Increased corneal thickness
- ✓ Epithelial defects
- ✓ Epithelial fragility
- ✓ Recurrent erosions
- ✓ Ulcers
- ✓ Edema
- ✓ Superficial punctate keratitis
- ✓ Delayed and incomplete wound repair
- ✓ Endothelial changes
- ✓ Neuropathy exemplified by reduced corneal sensitivity



EPITHELIAL ABNORMALITIES

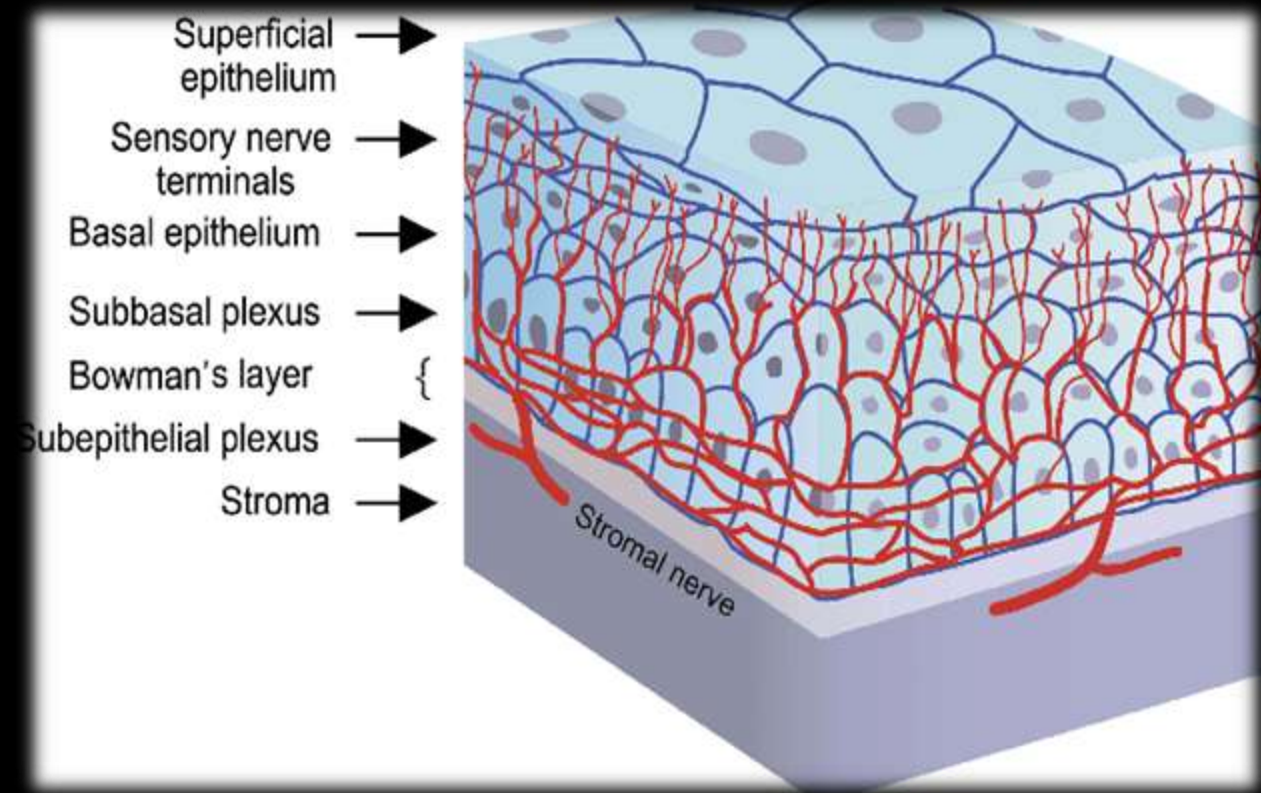
- Diabetic epithelial problems are often summarily referred to as *diabetic keratopathy* emphasizing the *major impact on corneal epithelium*.
- Signs of diabetic keratopathy include *epithelial fragility, defects and recurrent erosions, non-healing ulcers, corneal edema* due to altered epithelial barrier function, superficial *punctate keratitis*, abnormally slow and often incomplete *wound healing, lower cell density* especially in the basal layer, and increased susceptibility to injury.

BASEMENT MEMBRANE ABNORMALITY

- DM can also cause alterations in the *corneal epithelial basal cells* and *basement membrane*, leading to corneal *epitheliopathy* and *adhesion disorders*.
- DM also causes *production of abnormal basal lamina* and inadequate adhesion of epithelial cells to an abnormal basement membrane.

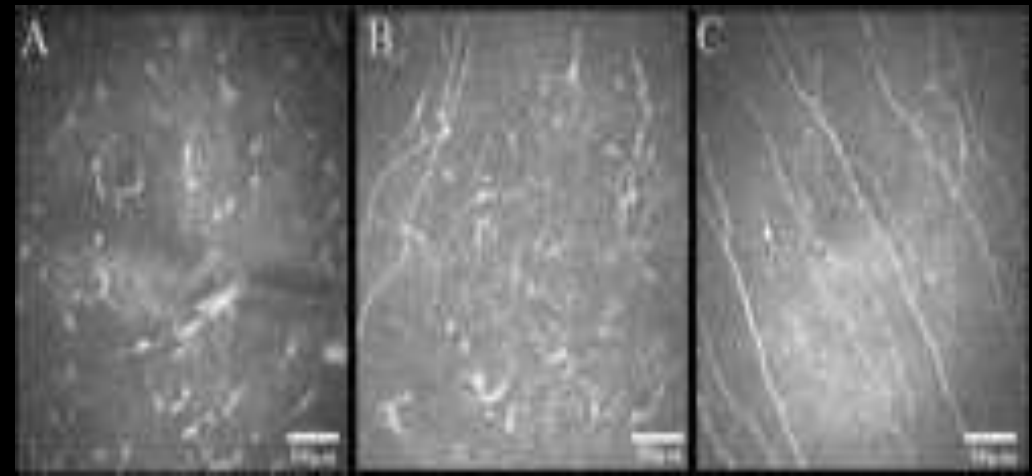
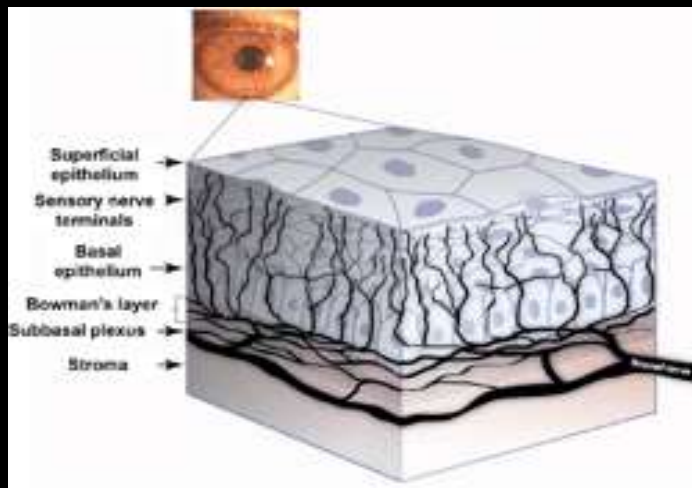
CORNEAL NERVE CHANGES

- *Decreased corneal sensitivity* in diabetic patients was already recognized.
- It is now well established that corneal sensitivity decrease is very common in diabetic patients. *Its degree correlates with the disease severity.*



NEUROPATHY

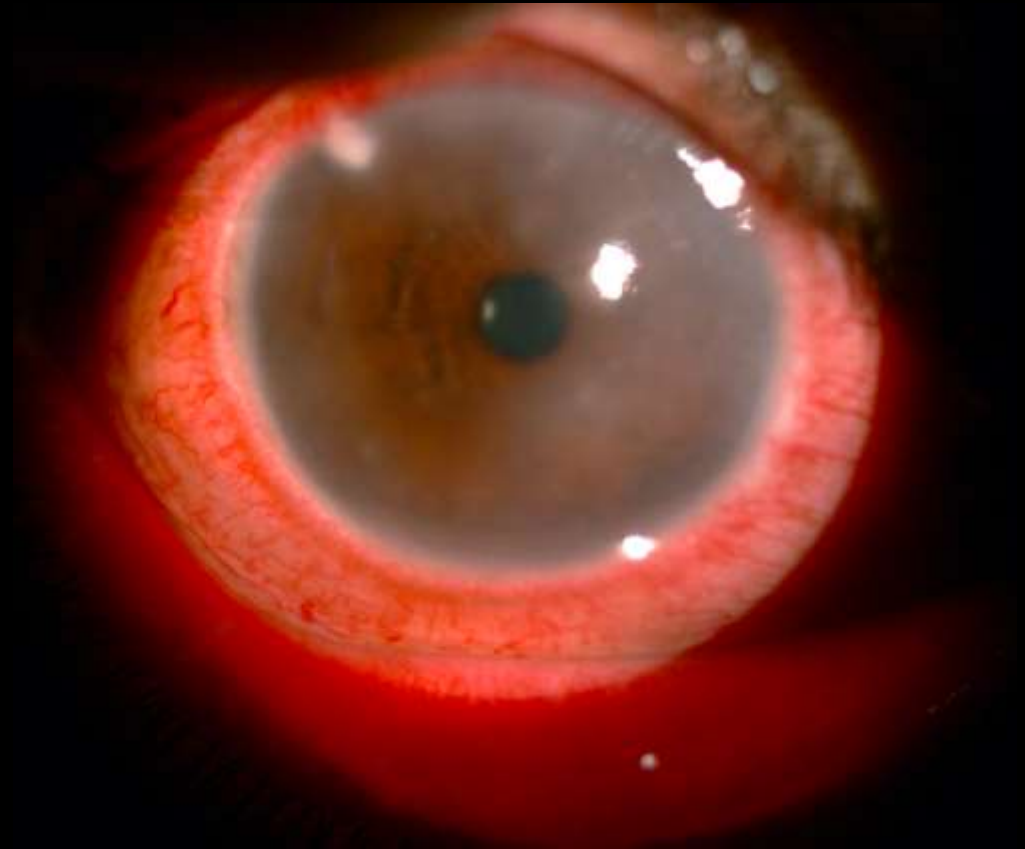
- *Diabetic neuropathy* is associated with *neurotrophic ulcerations of the skin and cornea*.
- The alterations of corneal sensitivity *can cause a dry eye* due to an absence or *reduction of the afferent reflex*, and *tear osmolarity may be increased*.



STROMAL CHANGES

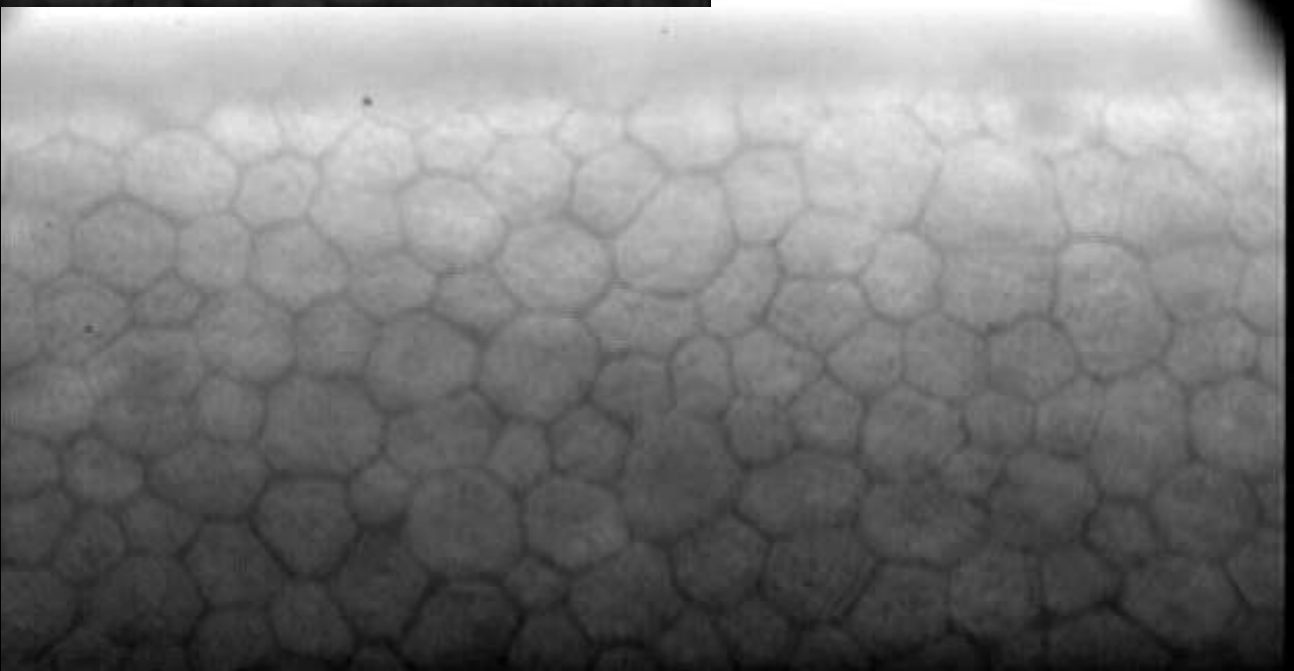
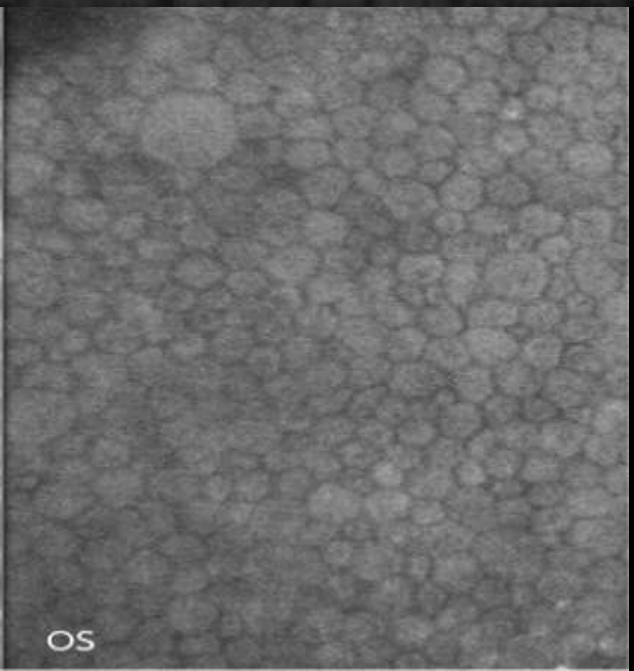
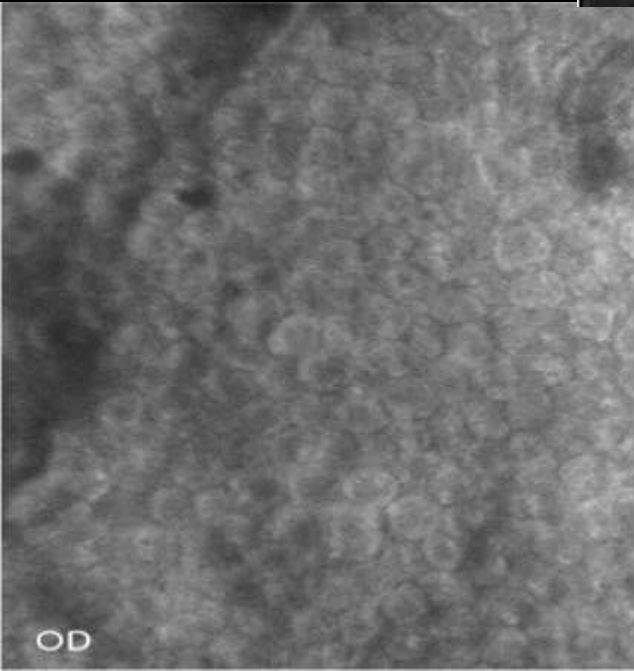
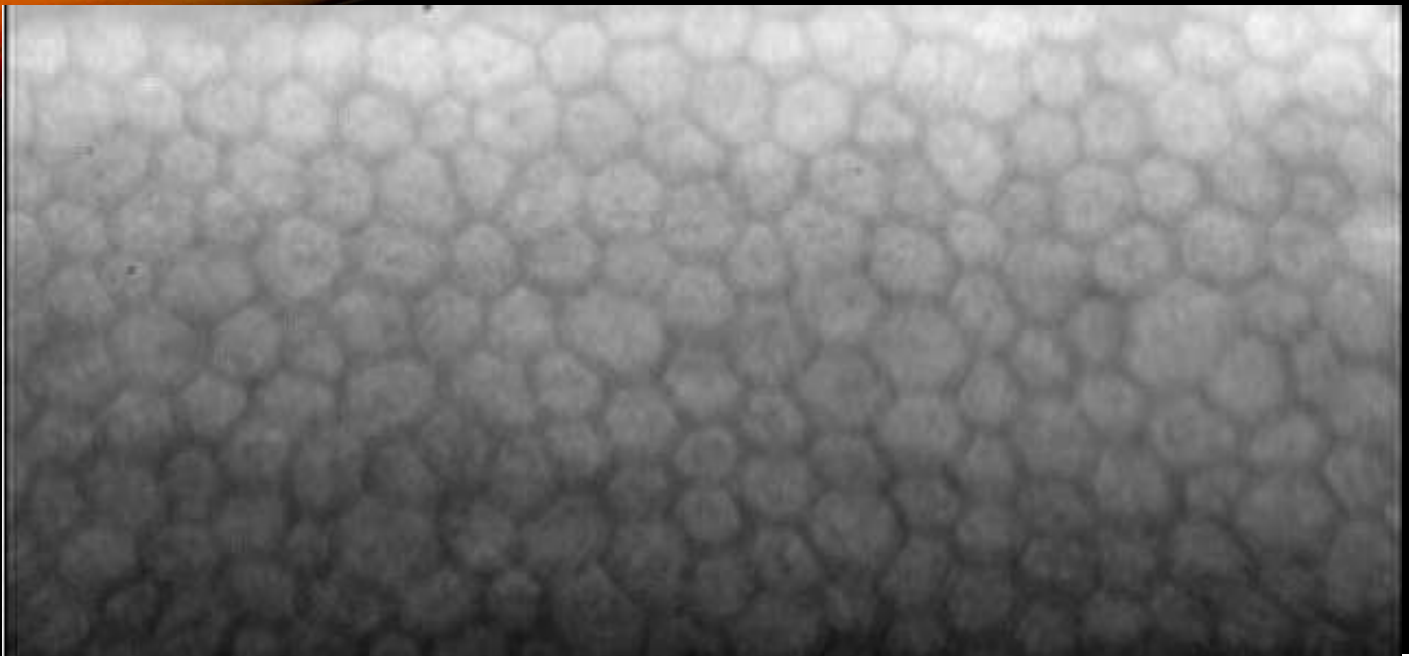
- *To date, there are only a few studies of the corneal stroma in diabetics.*
- *In patients with NIDDM corneal stroma acquires abnormal collagen fibril bundles of variable thickness.*

CORNEAL EDEMA



CORNEAL ENDOTHELIAL ABNORMALITIES

- *Several studies have evaluated the morphology, number and function of corneal endothelium in diabetic patients.*
- *Endothelial cell morphology is reportedly changed in diabetics with increased pleomorphism and variability of the cell area.*



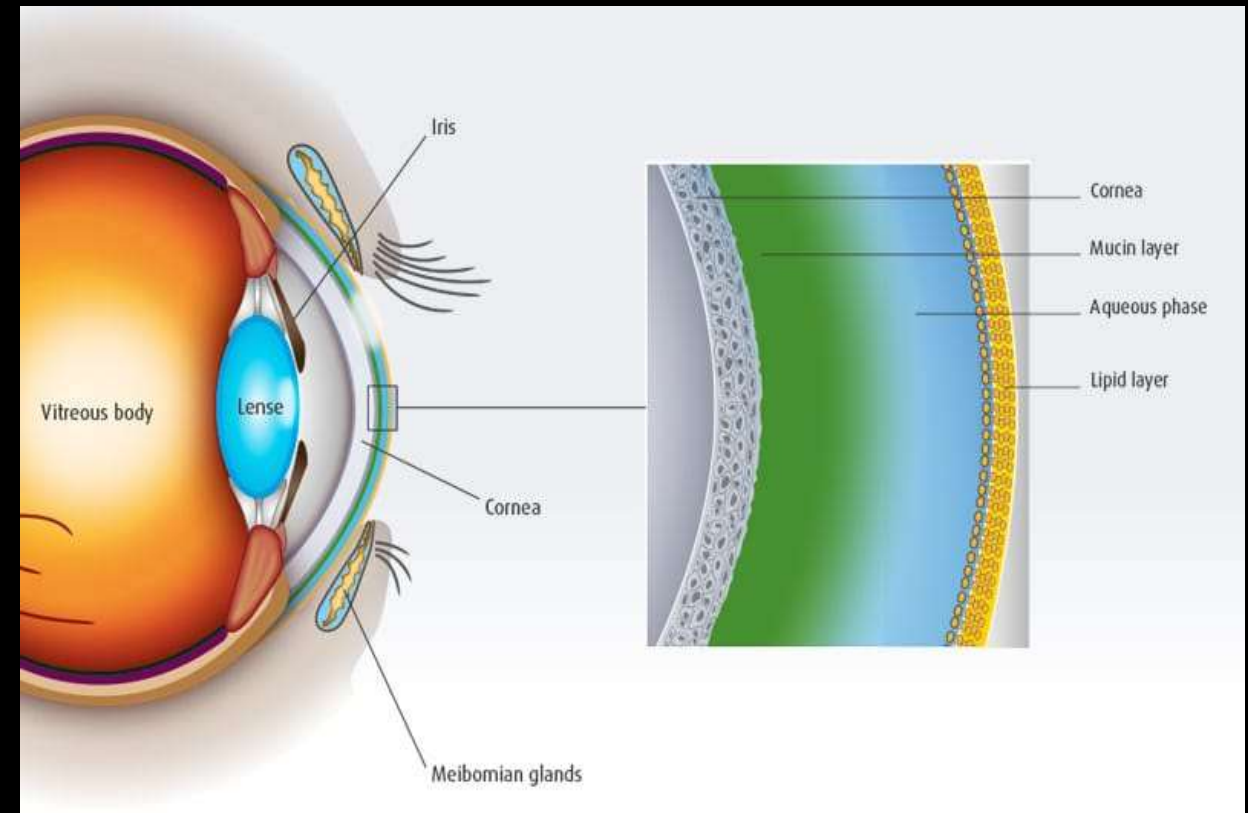
CONJUNCTIVAL INVOLVEMENT

- Abnormalities of the conjunctiva **are common** in diabetic patients.
- Problems specifically related to conjunctiva include **microvascular alterations** partly **similar to the retinal** ones, including **loss of capillaries, macrovascular dilation**, uneven vessel distribution, and **low numbers of goblet cells**.



TEAR FILM CHANGES

- Tear film plays a significant role in **corneal health** and **immune protection**.
- As a result, tear secretion in diabetics is often **significantly lower** than normal, and **dry eye incidence increases**.
- **Osmolarity** of diabetic tears also **increases**.

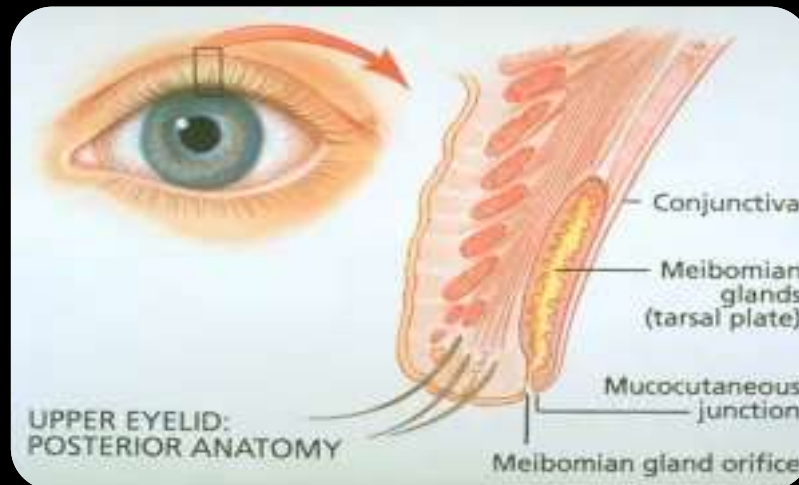


TEAR FILM ABNORMALITY IN DM

- *Substance P* plays a role in the maintenance of healthy ocular surface by *providing neurotrophic support* and promoting proliferation and migration of corneal epithelial cells.
- *Reduction in substance P* level may result in *impairment of corneal epithelial homeostasis*, potentially leading to exacerbation of corneal complications associated with DM.
- The tear *substance P* level was also shown to be related to the *duration of DM and severity of diabetic retinopathy*.

DM AND MEIBOMIAN GLAND DYSFUNCTION

- An experimental study revealed that insulin stimulated the proliferation of immortalized human meibomian gland epithelial cells in a dose-dependent manner, while *excess glucose resulted in progressive cell loss*.
- *Insulin deficiency and hyperglycemia may be toxic for the meibomian gland epithelial cells and increase the risk of meibomian gland disorders.*



SURGICAL PROBLEMS

- Structural and functional abnormalities in diabetic corneas contribute to an *increased risk of surgical complications*.
- Even with improved surgical techniques individuals with diabetes account for *80% of cases of corneal complications* after cataract and refractive surgery, vitrectomy, and PRP.



Refractive surgery including PRK and LASIK is more risky in diabetics because:

- ✓ Recurrent erosions
- ✓ Persistent epithelial defects
- ✓ Epithelial downgrowth
- ✓ Keratitis
- ✓ Poor wound healing
- ✓ Increased possibility of infections



THERAPY

Experimental therapeutics under development, including:

- *Topical naltrexone*
- *Topical insulin*
- *Inhibitors of aldose reductase*
- *Emerging gene*
- *Cell therapies*

Table 3

Potential new treatments for diabetic corneal disease.

| Treatment | System | Effect | Reference |
|---|---------------------------------------|--|-----------------------------|
| Thymosin β_4 eye drops | Diabetic patients | Reduction of chronic non-healing epithelial defects | Dunn et al., 2010 |
| Autologous serum drops | Diabetic patients | Increase of corneal wound healing | Schulze et al., 2006 |
| Topical CT-112 (ARI) | Diabetic patients | Improvement of corneal barrier function but not corneal sensitivity | Nakahara et al., 1995 |
| Insulin eye drops | Diabetic patients | Faster re-epithelialization after debridement for vitreoretinal surgeries | Bastion & Ling, 2013 |
| Insulin eye drops | Mouse IDDM | Prevention of subbasal nerve loss | Chen et al., 2013 |
| Insulin implants | Rat IDDM | Accelerated wound healing | Klocek et al., 2007 |
| Topical ranirestat (ARI) | Rat galactosemia | Faster epithelial wound healing; normalization of MMP-10 and integrin α_3 expression | Takamura et al., 2013 |
| IGF-I injections | Mouse NIDDM | Prevention of epithelial stem cell marker loss and increase in subbasal nerve density | Ueno et al., 2014 |
| Naltrexone (OGFR antagonist) eye drops | Mouse, Rat IDDM and NIDDM | Normalization of corneal epithelial wound healing, tear secretion, and corneal sensitivity | Sassani et al., 2016 |
| Antidiabetics nateglinide and glibenclamide | Rat NIDDM | Suppression of Descemet's membrane changes | Akimoto et al., 2008 |
| Ciliary neurotrophic factor | Mouse IDDM | Activation of LESC, increased nerve density, and promotion of epithelial healing | Zhou et al., 2015 |
| PARP inhibitor | Rat IDDM | Alleviation of delayed epithelial healing and decreased corneal sensitivity | Byun et al., 2015 |
| Topical nerve growth factor | Rat IDDM | Reduction of apoptosis and inflammation | Park et al., 2016 |
| IL-1 receptor antagonist | Mouse IDDM | Faster epithelial wound healing and sensory reinnervation, reduction in apoptosis, increase of Akt signaling | Yan et al., 2016 |
| Substance P | Mouse IDDM | Faster epithelial wound healing and reinnervation, reactivation of EGFR/Akt signaling | Yang et al., 2014 |
| Topical lacritin | NOD mice IDDM | Faster epithelial wound healing | Wang et al., 2014 |
| Intranasal curcumin in nanomicelles | Mouse IDDM | Promotion of wound healing and recovery of corneal sensation | Guo et al., 2016 |
| Gene therapy with AV | Human diabetic organ-cultured corneas | Faster epithelial wound healing, normalization of diabetic and LESC markers upon overexpression of c-met and silencing of MMP-10 and cathepsin F | Ljubimov & Saghizadeh, 2015 |
| Mir-146a inhibition | Human diabetic organ-cultured corneas | Faster epithelial wound healing, increase of EGFR and epithelial integrin $\alpha_3\beta_1$ | Winkler et al., 2014 |

ARI, aldose reductase inhibitor; PARP, poly(ADP-ribose) polymerase; NOD, non-obese diabetic; AV, adenovirus.

ANTERIOR SEGMENT NEOVASCULARIZATION

- ASNV includes angle neovascularization (**ANV**) and iris neovascularization (**INV**).
- It can lead to neovascular glaucoma (NVG) which is a severely blinding, intractable disease.
- The **retinal and choroidal ischemia/hypoxia** are considered the exciting factor for the development of **ASNV**.

PERIODIC SCREENING

- *Highlight the need for periodic screening of anterior segment diseases as well as retinal examination for patients with DM.*
- *An enhanced understanding in both patients and medical practitioners of the impact of DM on the anterior segment of the eye would be important for the optimal management of DM.*

Thank you

