



Diabetes

Impacts on the Cornea and Anterior Segment

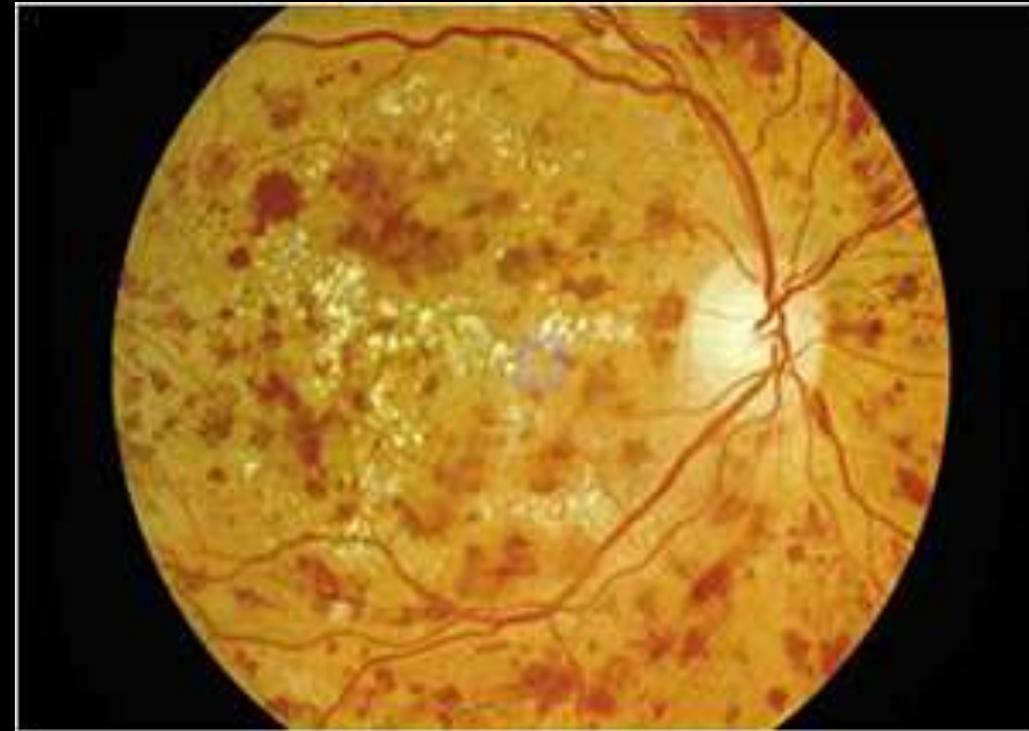
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GUMS

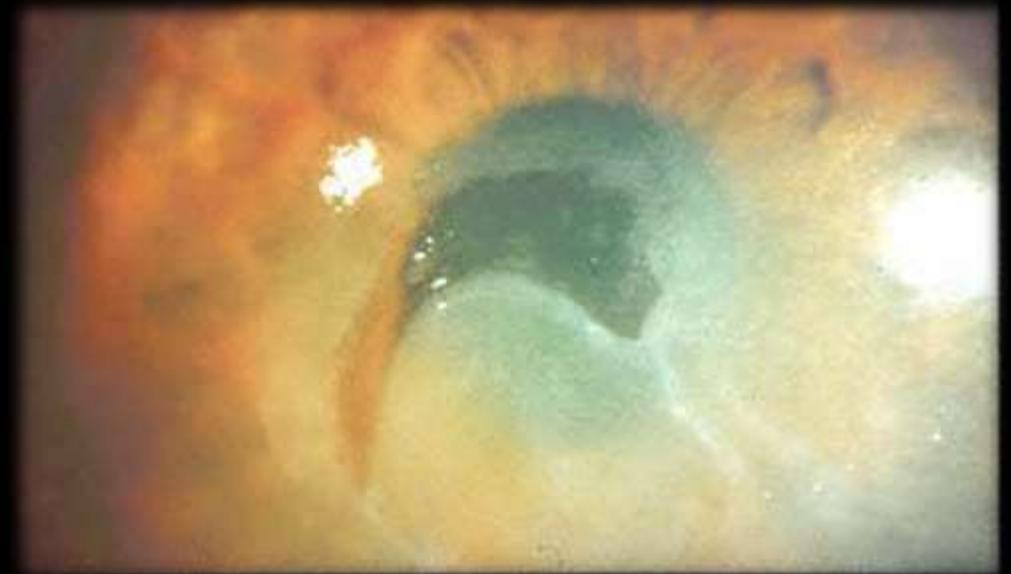
OCULAR DIABETES

- *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.*

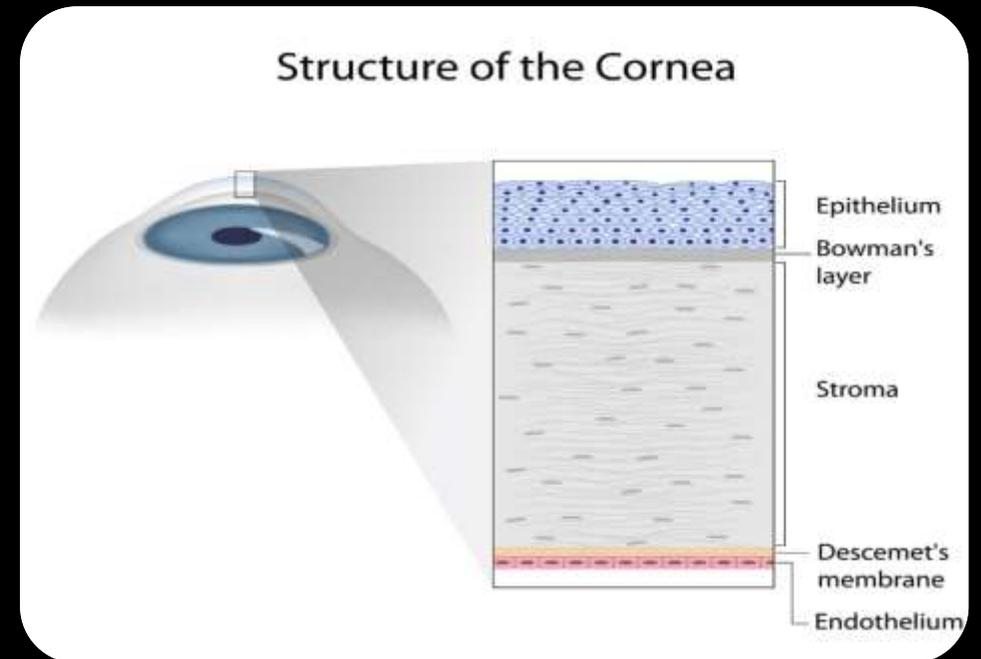
DIABETIC CORNEAL DISEASE

- *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

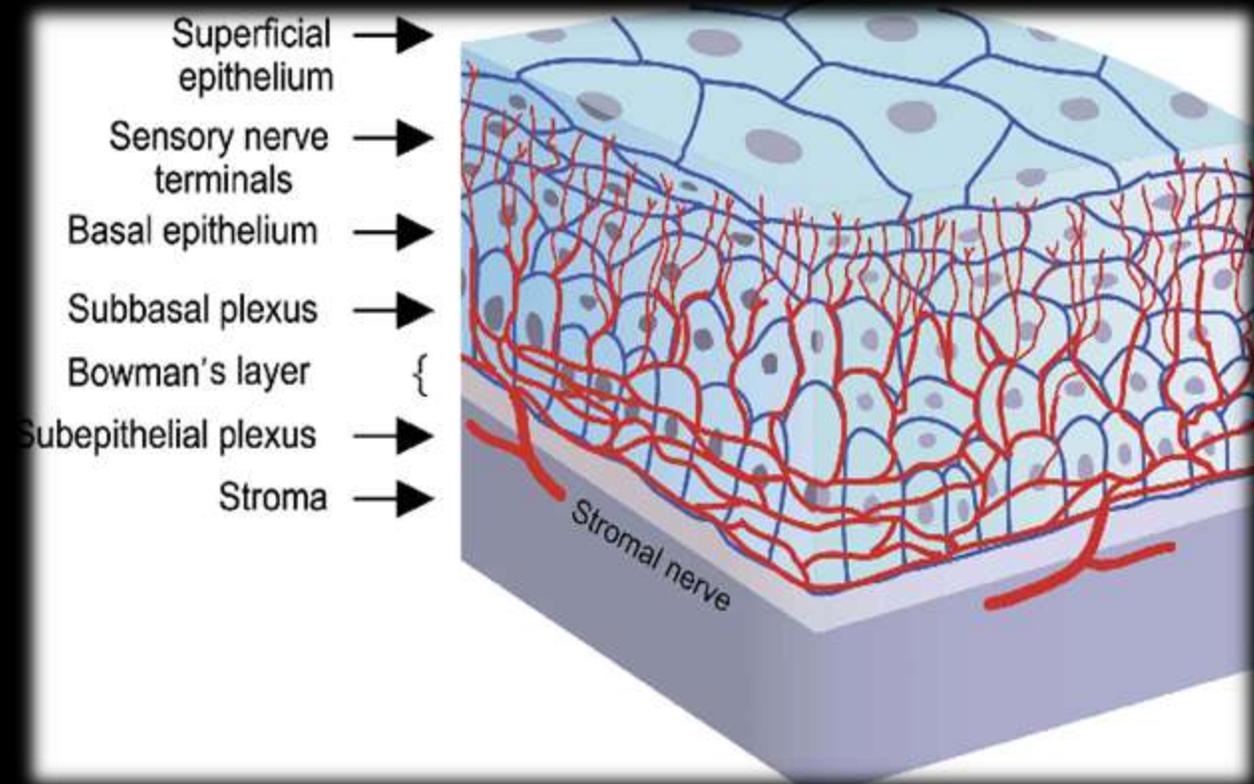
- Diabetic epithelial problems are often summarily referred to as *diabetic keratopathy* emphasizing the *major impact on corneal epithelium*.
- Signs of diabetic keratopathy include *epithelial fragility, defects and recurrent erosions, non-healing ulcers, corneal edema* due to altered epithelial barrier 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*.

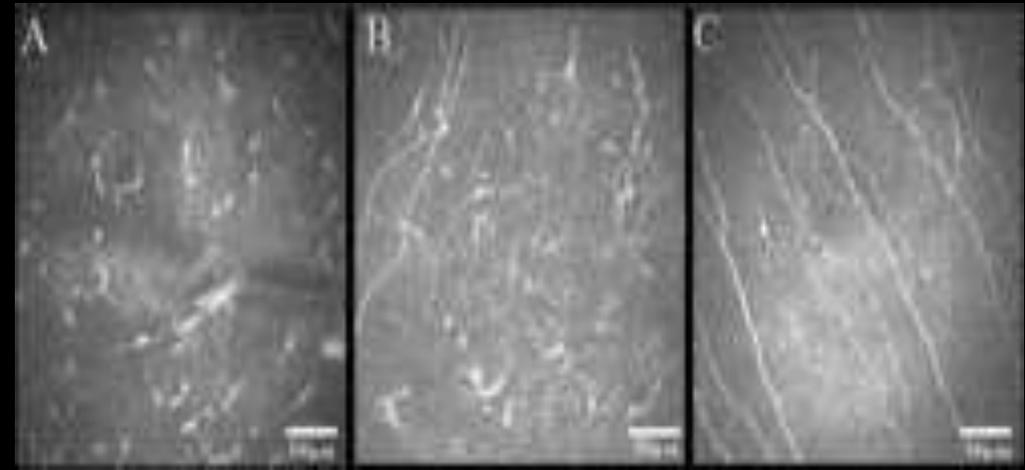
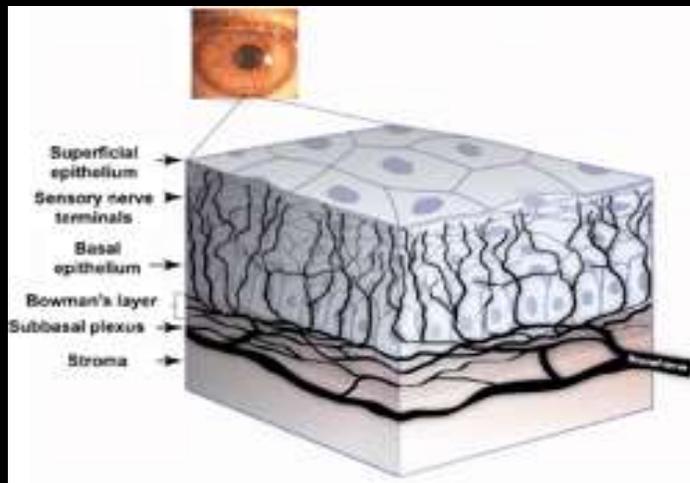
CORNEAL NERVE CHANGES

- *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

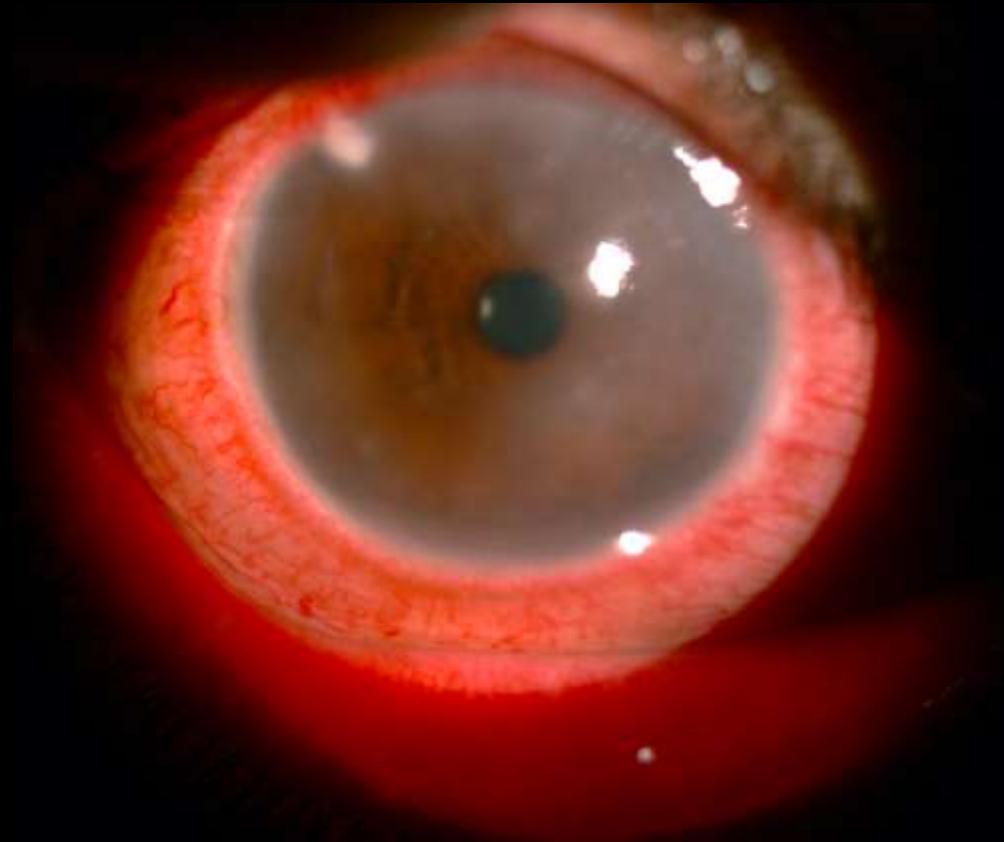
- *Diabetic neuropathy* is associated with *neurotrophic ulcerations of the skin and cornea*.
- The alterations of corneal sensitivity *can cause a dry eye* due to an absence or *reduction of the afferent reflex*, and *tear osmolarity may be increased*.



STROMAL CHANGES

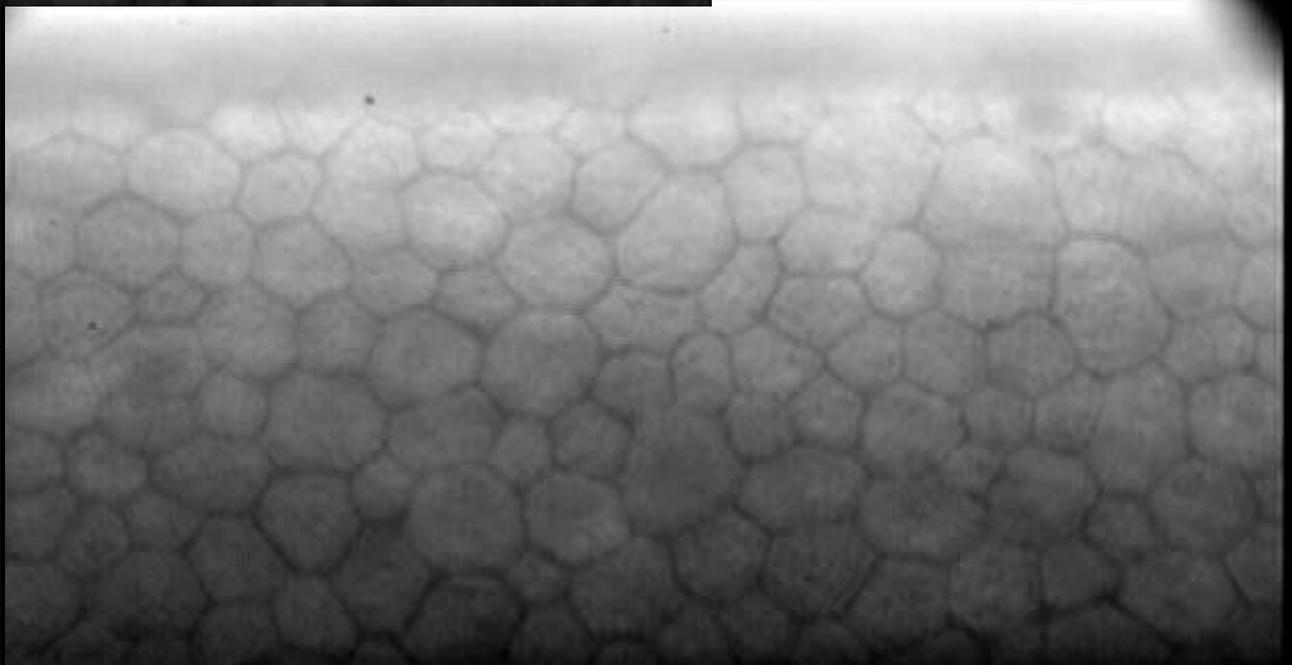
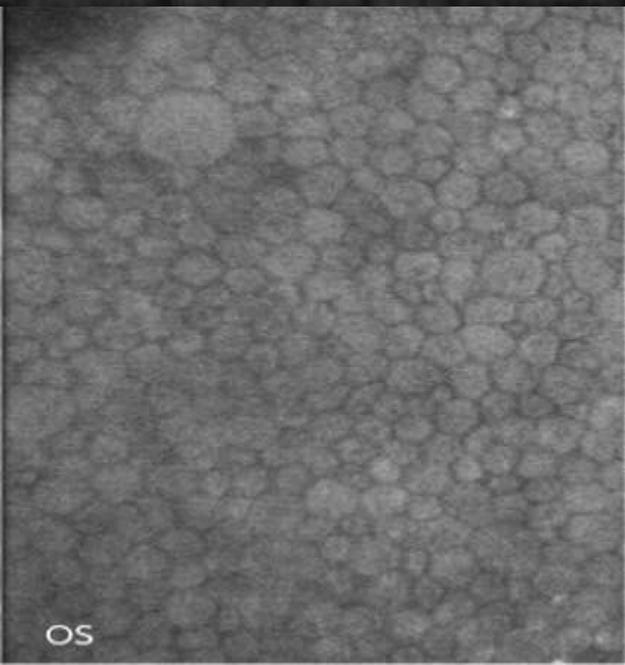
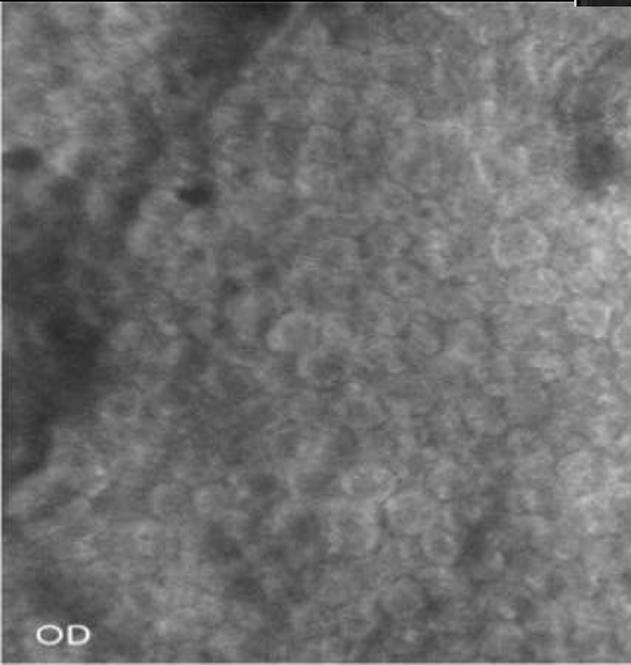
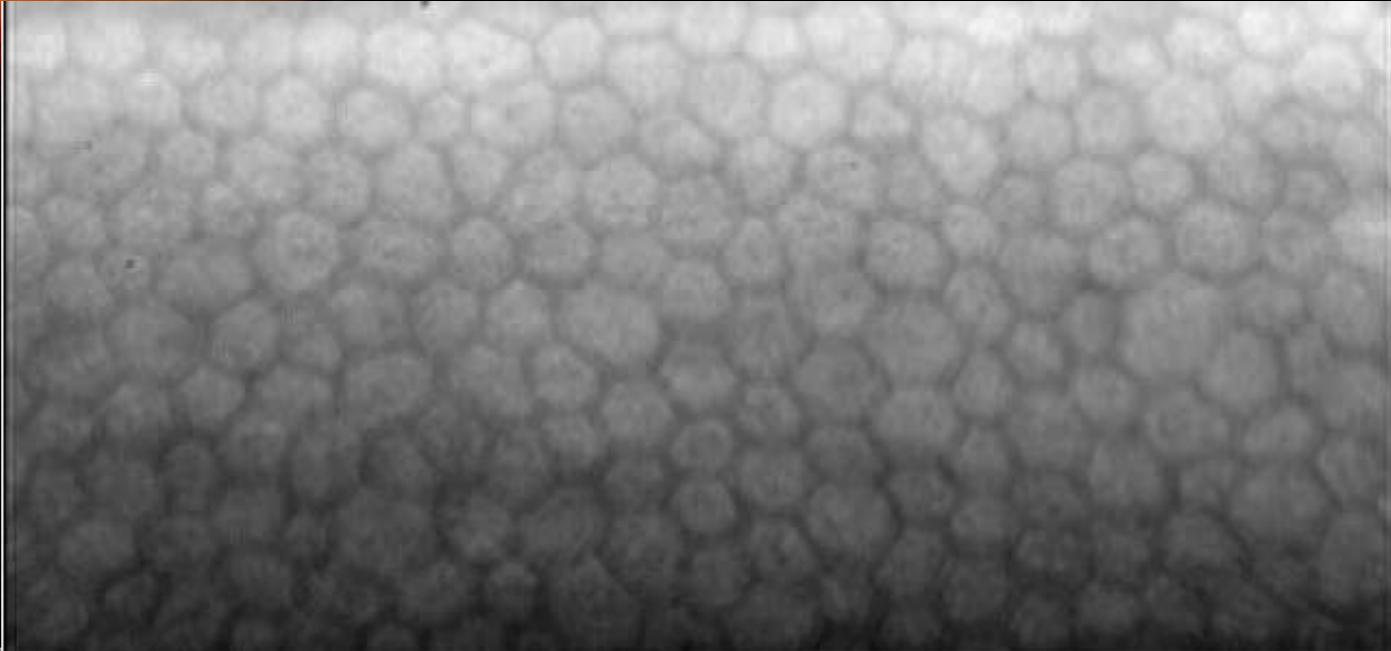
- *To date, there are only a few studies of the corneal stroma in diabetics.*
- *In patients with NIDDM corneal stroma acquires **abnormal collagen fibril bundles of variable thickness.***

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.*



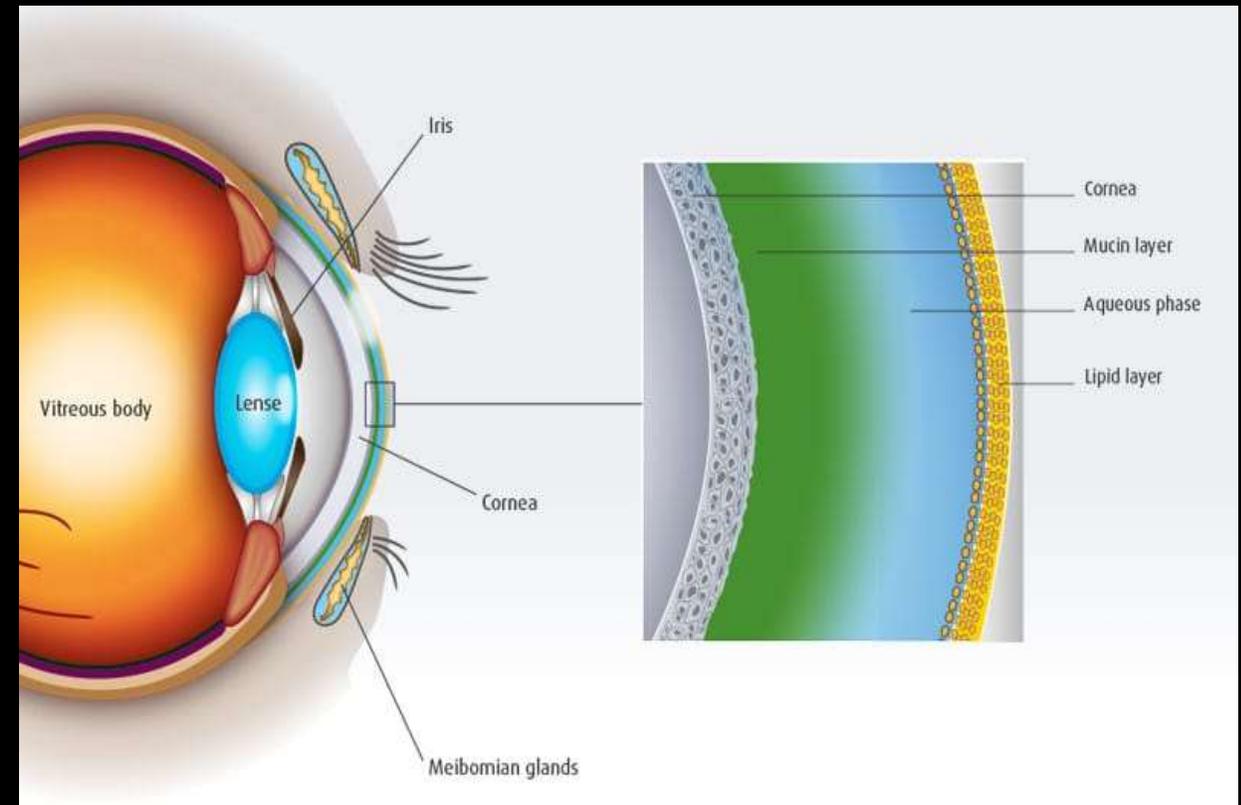
CONJUNCTIVAL INVOLVEMENT

- 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*.

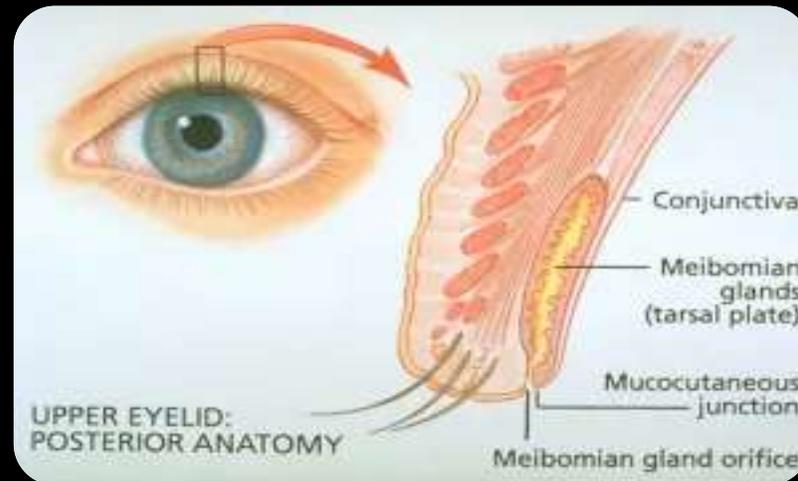


TEAR FILM ABNORMALITY IN DM

- *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

