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2 **Course Description**

- Diabetes can affect all structures of the eye, particularly the cornea, causing a condition known as diabetic keratopathy (DK). This presentation will provide a comprehensive overview on all the potential manifestations and complications of DK.

3 **Learning Objectives**

- Learn about how diabetes can affect the cornea causing a condition known as diabetic keratopathy (DK)
- Recognize the signs and symptoms of a DK patient
- Explore how chronic systemic hyperglycemia mechanistically affects each corneal layer and nerves
- Discuss traditional and new treatments for DK, as well as risk factors, differentials and complications
- Increase awareness of DK so clinicians can appropriately address, manage and treat diabetic patients during routine comprehensive diabetic eye exams

4 **Outline**

- Introduction
- Impact of diabetes on the cornea
- Treatment
- Risk factors
- Differential diagnosis
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6 **Diabetes and The Eyes**

7 **We need to pay attention to cornea for DM patients because.....**

Diabetes can lead to corneal disease or Diabetic Keratopathy!!

8 **History of DK**9 **Epidemiology of DK**

- DK Prevalence estimations:
 - ~1/3 of patients with DM (Rao, Ioli)
 - ~47-64% (Schultz, 1981)
 - Epithelial lesions: ~2/3 (Rao)
- DK is believed to have high incidence:
 - Rarely diagnosed (Wylegala)
 - Underreported (Kaji)
 - Overlooked
 - Not considered serious or pathological (Kaji)
 - Difficult confirming changes are only due to DM
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10 **Outline**

- Introduction
- Impact of diabetes on the cornea
 - Pre-corneal tear film
 - Epithelium (& basement membrane)
 - Stroma
 - Endothelium
 - Corneal nerves
- Treatment
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11 **Review of Cornea**12 **Review of Cornea**13 **THE PRE-CORNEAL TEAR FILM**14 **Tear Film Review**15 **Diabetes and Tear Film...**16 **Facts about Diabetes & Tear Film...**

- What some studies are finding!
- A healthy lipid layer reduces the rate of evaporation by 90-95% (Tasman)
- TBUT "in nearly all diabetics tested was found to be less than 10 seconds, a finding only seen in 5.8% of controls" (Seifart)

- ↓TBUT values correlate with “peripheral neuropathy and poorly controlled disease” (Dogru)
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17 **Take home point**

- Diabetes can reduce the effectiveness of tear film by altering structure and function causing....

18 **Review of Cornea**

19 **CORNEAL EPITHELIUM
&
BASEMENT MEMBRANE**

20 **Review of Epithelium**

21 **DM and Epithelium**

22 **Diabetic Keratoepitheliopathy**

Signs/Symptoms:

- Recurrent corneal erosion (Owen, Perry, Herse, Schultz 1981, 1984, Sato, Abdelkader)
- Slower wound repair (Hatchell, Herse, Sato)
- Delayed reepitheliazation (Kaji)
- SPK/Persistent epithelial defects (Herse, Owen, Schultz 1984)
- Increased epithelial fragility (Herse, Abdelkader)
- ↑ risk of infection (i.e. fungal keratitis)
- ↓ defense properties and barrier functions → edema (Gobbels, Yokoi, Gekka, Perry, Sato)
 - 5.4x's more permeable to water/ionic substances (Gobbels)
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23 **Diabetes and Epithelium**

- Is AGE only in epithelium?
 - Gradient of AGE: epithelium>stroma>endo
 - Metabolism is mostly dependent on the aqueous humor (Zou)
 - ↑expression of AGE productions, AGE receptors, and transcription factor nuclear factor kappa-B (NF-κB) in the lacrimal glands (Alves)
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24 **Take home point**

- Diabetes can produce excess AGE products that deposit in the epithelium altering structure and function causing Diabetic Keratoepitheliopathy

25 **Review of Cornea**

26 **CORNEAL STROMA**

Bypass Bowman's Layer and onto...

27 **Corneal Stroma**

Signs/Symptoms:

- Wide spaced collagen fibril matrix → ↓ transparency (Rehany)
- Transient stromal edema (Herse)
- Corneal lattice degeneration (Herse)
- Various forms of keratitis (Herse)
- Stromal ulceration/melting/perforation (Adbelkader, Lockwood)
- Stromal scarring (Adbelkader, Lockwood)
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28 **Review of Cornea**

29 **CORNEAL ENDOTHELIUM**

30 **Review of Endothelium**

31 **Diabetes and Endothelium**

32 **Diabetes and Endothelium**

Signs/Symptoms:

- Morphology (Structure)
 - Cell density
 - Pleomorphism (shape)
 - Polymegathism (size)
- Permeability (Function)
 - Pump function → corneal thickness
 - “May be one of the earliest changes detectable in the diabetic eye” (Busted)
 - Associated with “increased HbA1c and blood glucose levels, and severe retinal complications” (Busted, Su DHW)
- Descemet’s membrane:
 - Wrinkling of descemet’s membrane (Herse, Henkind)
 - Females more prone (Herse)
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33 **Comparing Endothelial Changes**

34 **Take home point**

- Endothelium is the “powerhouse” of the cornea
- Diabetes can cause irreversible, detrimental changes to the structure and function of endo cells
- Corneal thickness
 - May be earliest indicator of diabetes affecting eyes

- Associated with glucose fluctuations & severe retinal complications

35 CORNEAL NERVES AND SENSITIVITY

36 Review of Cornea

37 Review of Corneal Nerves

38 Diabetes and Corneal Neuropathy

- ↓ Corneal sensation + severe retinopathy linked to longer disease duration (Schuwartz, Saito)

39 Diabetes and Corneal Neuropathy

40 Diabetes and Corneal Neuropathy

41 Stages of Diabetic Corneal Neuropathy

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42 Clinical advice: DK & Nerves

Course of nerve changes...

- Mild to moderate neuropathy
 - OBJECTIVE change in long nerve fiber bundles
- Severe neuropathy
 - SUBJECTIVE ↓Corneal sensitivity
- Instruments are more sensitive! (Rosenberg)

Clinical Pearl:

- Consider diabetic corneal neuropathy when pts develop unexplained corneal epithelial disease and ulcer (Lockwood)
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44 Treatment Options

- Standard Treatments:
 - Preservative free topical lubricants
 - Bandage contact lens
 - Patching

- Tarsorrhaphy
- Induced ptosis
- Conjunctival flap
- Topical antibiotic
- Topical steroid

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45 **Treatment Options**

- New Treatments:
 - Topical insulin-like growth factor-1 and substance P (E)
 - Topical insulin (E) (H)
 - Topical nerve growth factor (E) (I) (H) (S)
 - Opioid growth factor (E) (S) (T)
 - Aldose Reductase Inhibitors (ARI)
 - Oral nicergoline (H)
 - Oral aminoguanidine (AGE) (A)
 - Oral goshajinkigan (ARI)

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47 **Risk factors**

- Tear
 - Stage of DK is a risk factor for abnormal lipid layer (Yokoi, Inoue 2001)
- Epithelium
 - Stage of DR is a risk factor for corneal epithelial fragility (Saini)
 - Stage of DK is a risk factor for dry eye findings (Yokoi, Inoue 2001)
- Stroma
 - >5 yrs of IDDM is a risk factor for abnormal stromal nerve architecture (He)
- Endothelium
 - Poor control of diabetes is a risk factor for abnormal endothelial findings (Herse, Busted, Su, DHW)
 - Stage of DR is a risk factor for abnormal corneal thickness, thicker in earlier stages of diabetes (Rosenberg, Busted, Su, DHW)
 - Duration of disease >10 years (Lee)
- Neuropathy/Sensitivity
 - DM is a risk factor for neurotrophic keratopathy (Lockwood, Hyndiuk)

- Duration of DM (Herse), poor control of diabetes (Herse) and more advanced stage of DR (Saito, Rogell) is a risk factor for abnormal corneal sensitivity
- >5years of IDDM is a risk factor for decreased epithelial nerve density (He)
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49 **Differential diagnosis**

50 **Outline**

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51 **Complications**

52 **Outline**

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53 **Summary of DK**

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- 1
 - Decrease tear break up time (TBUT)
 - Symptomatic dry eyes
 - Decreased
 - Epithelial defects
 - Superficial punctate keratitis
 - Persistent epithelial erosion/defects
 - Lacrimal gland damage
 - Decreased tear production/lacrimation
 - Decreased reflex tearing
 - Abnormal Schirmer test
 - Reduction in blink rate
 - Less inclined to use artificial tears
 - Decreased corneal healing/wound repair
 - Delayed reepitheliazation
 - Increased epithelial fragility
 - Decreased corneal sensitivity
 - Epithelial edema
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 - Stromal edema
 - Endothelial edema
 - Recurrent corneal erosion
 - Increase risk of infection
 - Reduction in corneal transparency
 - Transient stroma edema
 - Corneal lattice degeneration
 - Various forms of keratitis
 - Stromal ulceration (rare)
 - Stromal melting (rare)
 - Stromal perforation (rare)
 - Stromal scarring (rare)
 - Polymegathism
 - Pleomorphism
 - Wrinkling of descemet's membrane
 - Diabetic neurotrophic keratopathy
 - Blurry vision
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55 **We need to pay attention to cornea for DM patients because.....**

Diabetes can lead to corneal disease or Diabetic Keratopathy!!

56 Thank you

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