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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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- Summary

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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

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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• Complications
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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)

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)
  •

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)
  •

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)

Review of Cornea

CORNEAL ENDOTHELIUM

Review of Endothelium

Diabetes and Endothelium

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)
  ◦
  ◦
  ◦
  ◦

Comparing Endothelial Changes

Take home point

• Endothelium is the “powerhouse” of the cornea
• Diabetes can cause irreversible, detrimental changes to the **structure** and **function** of endothelial 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 (Schwartz, Saito)
39 Diabetes and Corneal Neuropathy
40 Diabetes and Corneal Neuropathy
41 Stages of Diabetic Corneal Neuropathy
   •
   •
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:
     o Preservative free topical lubricants
     o Bandage contact lens
     o Patching
- Tarsorrhaphy
- Induced ptosis
- Conjunctival flap
- Topical antibiotic
- Topical steroid

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
• >5 years of IDDM is a risk factor for decreased epithelial nerve density (He)

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49 Differential diagnosis

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51 Complications

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53 Summary of DK
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 reepithelialization
   - Increased epithelial fragility
   - Decreased corneal sensitivity
   - Epithelial edema
   - 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

2. 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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