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.

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 mechanismally 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

Outline
- Introduction
- Impact of diabetes on the cornea
- Treatment
- Risk factors
- Differential diagnosis
- Complications
- Summary
We need to pay attention to cornea for DM patients because......

Diabetes can lead to corneal disease or Diabetic Keratopathy!!

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Diabetes and The Eyes

History of DK
- Cornea/anterior segment abnormalities
- Delayed wound healing
- 1 risk of infection

Published: "Diabetic Keratopathy"
1850: Francois
1981: Richard Schultz
1900
1950
2000
1967: Collier

Published: comprehensive review on DK
- Focus: pathophenomonic forms of DK used for early diagnosis
Epidemiology of DK

- DK Prevalence estimations:
  - ~1/3 of patients with DM (Kan et al)
  - ~47-64% (Sroka, 1981)
- Epithelial lesions: ~2/3 (Kan)
- DK is believed to have high incidence:
  - Rarely diagnosed (Ignacio)
  - Underreported (Kan)
  - Overlooked
  - Not considered serious or pathological (Kan)
  - Difficult confirming changes are only due to DM

Outline

- Introduction
- Impact of diabetes on the cornea
  - Pre-corneal tear film
  - Epithelium & basement membrane
  - Stroma
  - Endothelium
  - Corneal nerves
- Treatment
- Risk factors
- Differential diagnosis
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Review of Cornea

[Diagram of the cornea layers: Tear film, epithelium, stroma, basement membrane, Descemet's membrane, Endothelium]
THE PRE-CORNEAL TEAR FILM

Diabetes and Tear Film...

- Diabetic neuropathy
- Hyperglycemia
- Corneal sensitivity
- Changes in tear composition/chemistry
- Non-uniform lipid
- Goblet cell loss
- TBUT
- Tear spreading/stability
- Evaporative dry eye
- Dry eye symptoms
- Epithelial disease
- Compromised/Delayed healing

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” (Searle)
- ↓TBUT values correlate with “peripheral neuropathy and poorly controlled disease” (Degra)
Take home point

- Diabetes can reduce the effectiveness of tear film by altering structure and function causing:
  
  - Dry eyes
  - Decreased corneal sensitivity
  - Damage corneal nerves

Review of Cornea

Review of Epithelium

CORNEAL EPITHELIUM & BASEMENT MEMBRANE
DM and Epithelium

Diabetes Mellitus

Sugar + Amino acid

Mallard Reaction (High heat)

Advanced Glycation End (AGE) Product

Deposits in epithelium

Changes in epithelial cells & Basement Membrane

Diabetic Keratoepitheliopathy

Diabetic Keratoepitheliopathy

**Signs/Symptoms:**
- Slower wound repair (Hatchell, Horne, Sato)
- Delayed reepithelization (Kaji)
- SPK/Persistent epithelial defects (Horne, Owen, Schultz 1984)
- Increased epithelial fragility (Horne, Abdelkader)
- ↑ risk of infection (i.e. fungal keratitis)
- ↓ defense properties and barrier functions → edema (Gebbels, Youse, Gokko, Perry, Sato)
- 5.4x’s more permeable to water/ionic substances (Gebbels)

Diabetes and Epithelium

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

Take home point

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

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**Corneal Stroma**

**Signs/Symptoms:**
- Wide spaced collagen fibril matrix → ↓ transparency (transparency)
- Transient stromal edema (transient)
- Corneal lattice degeneration (transept)
- Various forms of keratitis (transient)
- Stromal ulceration/melting/perforation (transient)
- Stromal scarring (transient)

**Image:**
- Stroma layers: collagen fibrils, keratocytes, Descemet's membrane, Endothelium
CORNEAL ENDOTHELIUM

Diabetes and Endothelium

Diabetes Mellitus
  ↓
Hyperglycemia
  ↓
Glucose
  ↑
Aldose Reductase
  ↓
Glyceraldehyde
  ↓
Krebs Cycle
  ↓
ETC

Overhydrated End Cell
  ↓
Endo well
  ↓
Slow down Krebs Cycle

Permeability Changes

Morphological Changes

Diabetes and Endothelium

Review of Endothelium

• Single layer
• Metabolically active
• Hydration of cornea

Diabetes and Endothelium

Signs/Symptoms:
  • Morphology (Structure)
    • Cell density
    • Pleomorphism (shape)
    • Polymegathism (size)
  • Permeability (Function)
    • Pump function \(\rightarrow\) corneal thickness
      - "May be one of the earliest changes detectable in the diabetic eye" (source)
      - Associated with "increased HbA1c and blood glucose levels, and severe retinal complications" (source)
  • Descemet’s membrane:
    • Wrinkling of Descemet’s membrane (source)
    • Females more prone (source)
Comparing Endothelial Changes

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Cell Diameter</th>
<th>Cell Density</th>
<th>Irregularity</th>
<th>CV of cell size</th>
<th>Polarity</th>
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<tbody>
<tr>
<td>Schilli et al</td>
<td>Type 2</td>
<td>25/23</td>
<td>Increased</td>
<td>Increased</td>
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<tr>
<td></td>
<td>Type 1</td>
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<td>NA</td>
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<td>Hal et al</td>
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<td>No difference</td>
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<td>Increased</td>
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<td>Increased</td>
<td>NA</td>
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<tr>
<td>Charalampidis</td>
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<td>Increased</td>
</tr>
<tr>
<td>Rockmore et al</td>
<td>Type 1 &amp; 2</td>
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<td>Decreased</td>
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<td>NA</td>
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<tr>
<td>Terri et al</td>
<td>Type 2</td>
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<td>Decreased</td>
<td>No difference</td>
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<tr>
<td>Ubhay et al</td>
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</tr>
</tbody>
</table>

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

CORNEAL NERVES AND SENSITIVITY

Review of Cornea

- Tear film
  - Surface flat cells
  - Polygonal cells
  - Basal cell layer
- Bowman's membrane
- Collagen fibrils
- Keratocytes
- Descemet's membrane
- Endothelium

1/3 of anterior stroma
Review of Corneal Nerves

Long posterior ciliary + anterior ciliary nerve

Ophthalmic division of trigeminal nerve

Diabetes and Corneal Neuropathy

- ↓ Corneal sensation + severe retinopathy linked to longer disease duration

Corneal scarring

Diabetes and Corneal Neuropathy

Diabetes affects the nerves

Epithelial defects

- Corneal infection/trauma
- Wound healing
- Corneal ulcers
- Corneal scarring
Instruments are more sensitive!

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

Clinical Pearl:
- Consider diabetic corneal neuropathy when pts develop unexplained corneal epithelial disease and ulcer (Levenson)

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Treatment Options
- Standard Treatments:
  - Preservative free topical lubricants
  - Bandage contact lens
  - Patching
  - Tarsorrhaphy
  - Induced ptosis
  - Conjunctival flap
  - Topical antibiotic
  - Topical steroid
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)

Outline

- **Risk factors**
  - Tear
  - Sale of DK is a risk factor for abnormal lipid layer (Nakamura, 2001)
  - Epithelium
  - Sale of DK is a risk factor for corneal epithelial fragility (Nakamura, 2001)
  - Sale of DK is a risk factor for dry eye findings (Nakamura, 2001)
  - Stromas
  - Sale of IODM is a risk factor for abnormal stromal nerve architecture (Nakamura, 2001)
  - Endothelium
  - Sale of DK is a risk factor for abnormal endothelial findings (Nakamura, 2001)
  - Sale of DK is a risk factor for abnormal corneal thickness, thicker in earlier stages of disease (Kawamura, 2001)
  - Duration of disease >10 years (Nakamura, 2001)
  - Neuropathy/Sensitivit
  - Sale of DK is a risk factor for neurotrophic keratopathy (Kawamura, 2001)
  - Duration of DK, poor control of diabetes (Nakamura, 2001) and more advanced stage of DR (Nakamura, 2001) is a risk factor for abnormal corneal sensitivity
  - Sale of IODM is a risk factor for decreased epithelial nerve density (Nakamura, 2001)

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Stroma/Neuropathy:
- Stromal dystrophies
- Infection
- Autoimmune
- Toxicity

In general:
- Aging changes
- Trauma
- Extended CL wearer

Complications

Surgical
- Cataract surgery
- Dislocation lens
- Corneal edema
- Cloudy corneal epithelium
- New/recurrent epithelial erosion
- Corneal epitheliopathy
- PK/PK
- Persistent clinical corneal changes
- Severe/rapid TBUT
- Predisposition to bacterial and fungal infection
- Leuk
- Poor refractive outcomes
- Epithelial complications
- Epithelial ingrowth
- Neovascularization of iris and angle
- Microscopy/PRP
- Prolong/recurrent epithelial defects

Trauma
- Corneal abrasion
- Deeper damage
- New/recurrent corneal erosion

Contact Lens
- Microbial keratitis
- Corneal ulcer
- Ocular infection
- Increased lens opacification
- Resistance to corneal edema
- Non-resolving corneal edema

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Amiee Ho, O.D.
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References

- Sato, Euchi, MD, Fumihiko Mori, MD, PhD, Sho Igarashi, MD, Tohru Abiko, MD, PhD, Masumi Takeda, MD, PhD, Satoshi Ishik o, MD, PhD, and Akitoshi Yoshida, MD.
- Am J Ophthalmol
- Invest Ophthalmol Vis Sci
- Van Ort SR, Gerber RM. Topical application of insulin in the t reatment of decubitus ulcers: a pilot study. 
- Boll Ocul Cornea
- Growth factor-1.
- Boll Ocul Cornea
- References