CORNEAL PATHOLOGY IN DIABETES

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CASE STUDY

- 59 year-old Caucasian male with Type II DM
- Peripheral neuropathy
- Blind in his left eye – childhood trauma
- POAG on Bimatoprost – IOP 14 mmHg
- Routine phaco + PCIOL January 2016
- Independent and driving – had 6/9 (20/25) vision post-op
- Developed a non-healing epithelial defect
Case Study

Referred to Corneal Service April 2016

- Continued care by MR team
- Copious lubrication
- Scleral contact lens
- AMT
- Botox tarsorrhaphy
- Autologous serum or FAB
SUBCLINICAL ABNORMALITIES

- a decrease in epithelial barrier function
- abnormalities in shape of epithelial and endothelial cells
- basement membrane thickening
- Increased central corneal thickness in diabetic patients was reported to be associated with increased HbA1c and blood glucose levels, and severe retinal complications.
- decreased corneal sensation
STRUCTURAL ABNORMALITIES IN EPITHELIUM/ BASEMENT MEMBRANE COMPLEX

- Lack of Type IV anchoring collagen fibrils
- Thickening and multi-lamination of the basement membrane
- Deposition of AGE’s (advanced glycation end products) in BM
  - BM loses adhesive property
  - Epithelial cells lose the clue for attachment to BM
Corneal innervation

**Nerve supply of Cornea**

- Cornea is rich in sensory nerve supply derived from ophthalmic division of trigeminal which give branch to;
  - Nasociliary nerve and
  - Ciliary nerves (terminal branch)

- Ciliary nerve enter the pericoroidal space a short distance behind the limbus.
- 60-80 myelinated branches pass into cornea
Corneal Innervation

- 70 to 80 large diameter myelinated nerves
- Enter at posterior to mid-stromal level
- Run radially and anteriorly toward the center of the cornea.
- Anterior stromal layers are innervated by multiple branches of these nerves
- Penetrate the cornea approximately 1 mm from the limbus, pass through Bowman's membrane, and turn in a clockwise direction forming the subbasal nerve plexus that lies between Bowman's layer and the epithelium forming the subbasal nerve vortex.
- Its geographic center is located between 2.18 and 2.92 mm from the corneal apex
CORNEAL INNERVATION

300 – 400 times more sensitive than either the tooth or the skin
Particularly sensitive along the horizontal meridian and less so along the vertical meridian
Pathophysiology of Neurotrophic Keratopathy

Theory:

• Loss of afferent sensory input leads to diminished lacrimal secretion, reduced nutritional support, and a dry ocular surface.

• The combination of a dry ocular surface and loss of trophic factors leads to epithelial breakdown.

CORNEAL ANAESTHESIA

- increases the risk of contact lens-related microbial keratitis
- superficial punctate keratitis, recurrent corneal erosions, persistent epithelial defects and corneal endothelial damage.
- Neurotrophic keratitis
- correlation between the severity of keratopathy and the patients' diminished peripheral sensation
- epithelial defects another manifestation of generalized polyneuropathy
Sensory neurons directly influence the integrity of the corneal epithelium.

- Neuronal destruction → Epithelial cells swell
- Abnormal basal lamina → Lose microvilli
- Slow or halt mitosis, which leads to epithelial breakdown.
Dry Eye

- Decreased goblet cells in conjunctiva – decreased TBUT
- Worsened after PRPC due to damage to LPCN
- Corneal anaesthesia – impaired reflex secretion
- Accumulation of AGE’s – increased inflammation associated with dry eye
- Impaired microvascular supply to lacrimal gland in long standing disease – poor lacrimation
# Neurotrophic Factors in Cornea

<table>
<thead>
<tr>
<th>Growth Factor</th>
<th>Function</th>
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</thead>
<tbody>
<tr>
<td>Nerve growth factor (NGF)</td>
<td>Critical for corneal nerve survival and maintenance, axonal branching, elongation, neuronal sprouting, and regeneration</td>
</tr>
<tr>
<td>Found in corneal epithelum and stromal keratocytes</td>
<td></td>
</tr>
<tr>
<td>Keratocyte growth factor (KGF)</td>
<td>Stimulates corneal epithelial proliferation, acts specifically on cells of epithelial origin</td>
</tr>
<tr>
<td>Expressed in stromal keratocytes</td>
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<tr>
<td>Ciliary neurotrophic factor (CNTF)</td>
<td>Promotes corneal epithelial wound healing by activating corneal epithelial stem/progenitor cells</td>
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<td>Transforming growth factor-α (TGF-α), interleukin-1β (IL-1β), and platelet-derived growth factor-B (PDGF-B)</td>
<td>Exclusively expressed in the corneal stroma TGF-α and IL-1β can upregulate the transcription of neurotrophins, such as NGF</td>
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</table>
**Corneal Sensation**

- Decrease in the corneal sensation\textsuperscript{23} and loss of nerve derived trophic factor
- Insulin-like growth factor 1 (IGF-1) and substance P, a neuropeptide present in sensory nerves, accelerate corneal epithelial wound healing.\textsuperscript{24}
- Topical application of substance P and IGF-1 accelerated the corneal epithelial wound healing process in diabetic animals.
- Topical medications that may result in anesthesia include timolol, betaxolol, sulfacetamide and diclofenac sodium, long term contact lens wear.
Stage 1

- mild, nonspecific signs and symptoms, including rose bengal staining of the inferior palpebral conjunctiva
- viscosity of the tear mucus increases.
  - decreased tear break-up time, leading to dry spots on the epithelium (Gaule spots)
  - resultant vascularization and scarring
- preservative-free artificial tears and ointments
- punctal occlusion.
- topical medications should be discontinued if possible.
STAGE 2

- nonhealing corneal epithelial defect.
- epithelium becomes loose, Descemet’s membrane develops folds as the stroma swells and becomes edematous.
- punched-out oval or circular shape. edges of the defect may become smooth and rolled with time.
- epithelial defect must be treated in order to prevent a corneal ulcer from developing and to promote healing.
- Prophylactic antibiotic drops preservative-free artificial tears.
- lateral tarsorrhaphy
- an injection of botulinum A toxin into the upper eyelid
- amniotic membrane transplantation over the epithelial defect.
Stage 3

- if stages 1 and 2 are not treated appropriately.
- stromal melting leading to perforation.
- often asymptomatic because of decreased corneal sensation

- immediate attention in order to stop the stromal lysis and prevent perforation.
- topical collagenase inhibitors such as N-acetylcysteine, tetracycline
Suspect of neurotrophic keratitis

- Corneal sensitivity testing
  - Normal → NK unlikely
  - Reduced
    - Vital staining, tear function tests, lid evaluation, nerve imaging, limbal evaluation, microbiology exams

- NK severity staging
  - Treat associated ocular surface diseases
    - Corneal perforation
      - Glue, amniotic membrane transplantation, conjunctival flap, keratoplasty
    - NK stage 3
    - NK stage 2
      - Tarsorrhaphy, conjunctival flap
    - NK stage 1
      - Avoid preservatives, artificial tears
DIABETES & INFECTION RISK

- Impaired neutrophil chemotaxis, phagocytosis and intracellular bactericidal activity
  - delayed wound healing
- Impaired immune response often exacerbated by vascular insufficiency
- Correlated with higher HbA1c levels, longer duration of disease, and the presence of diabetic retinopathy
- Weakened barrier - more prone to the development of corneal infections such as fungal keratitis
INFECTIVE FUNGAL KERATITIS
• .......can be fraught with problems

• Poor wound healing & corneal anaesthesia can make penetrating keratoplasty challenging

• Risk of persistent epithelial defects can result in loss of corneal graft

• Cataract surgery with arcuate keratotomies – severe and prolonged dry eye post-operatively
PATHWAY MECHANISMS TO PATHOLOGY

Increase in the polyol pathways

Deposition of advanced glycation end products
- Decrease in polyol and inhibition of aldose reductase activity using aldose reductase inhibitor (ARI)

- Effective in inhibiting the loss of corneal sensation
- Delaying corneal epithelial wound healing
- Restore endothelial barrier function but do not protect against the development of SPK’s
**Figure 5**

- **AGE in ECM (collagen)**
- **Soluble AGE**

**AGE Receptors**

- **Endothelial cells**
  - ROS production
  - NF κB production
  - Transcription enhanced

- **Macrophages**
  - Secretion of IL1
  - Secretion of TNF alpha

- **Enhanced permeability**
- **Proliferation fibroblasts and SMC**
- **Synthesis ECM**
- **Procoagulant effects**
  - (reduction in thrombomodulin activity, increase in tissue factor)
Novel Pharmaceuticals

- growth factors and cytokines can significantly enhance epithelialization (epithelial proliferation and migration) and consequently accelerate wound healing,
- local/topical administration of insulin, naltrexone (opioid antagonist) and nicergoline (ergoline derivatives) were found to improve, and significantly increase, the corneal wound healing rate.
- Aminoguanidine, Atorvastation inhibits deposition of AGE’s
- a new generation of ophthalmic pharmaceuticals for the treatment of diabetic keratopathy
NALTREXONE

- An opioid antagonist leads to accelerated DNA synthesis, cell replication, and tissue repair.
- NTX accelerated corneal re-epithelialization in organ cultures of human and rabbit cornea.
- Systemic application of NTX to the abraded corneas of rats, and topical administration of NTX to the injured rabbit ocular surface, increased re-epithelialization.
- Systemic injections or topical administration of NTX facilitates re-epithelialization of the cornea in diabetic rats.
**Potential Rx for OSD in Diabetics**

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<th>Mechanism of Action</th>
<th>Potential Treatment</th>
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<tr>
<td>Antioxidant</td>
<td>Vitamin C, Vitamin E</td>
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<tr>
<td>Anti-inflammatory</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Mitogenic &amp; neurotrophic</td>
<td>NGF, Substance P</td>
</tr>
<tr>
<td>Secretagogue</td>
<td>Pilocarpine</td>
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<tr>
<td>Supression of MMP’s</td>
<td>Tetracycline</td>
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<td>Tear replacement</td>
<td>Autologous serum</td>
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CASE STUDY

- Preservative free medication
  - Toxicity from chronic use of topical ocular medications also may cause nerve damage and resultant corneal anesthesia
- Recognise that previous laser had damaged long ciliary nerves
  - Diabetic patients who undergo panretinal photocoagulation receive a secondary insult to the ciliary nerves
- Peripheral neuropathy and keratopathy often go hand in hand
- Punctal occlusion
- Anterior stromal puncture
- Change Bimatoprost to PF GanFort
CASE STUDY

Middle-aged male, blind in one eye

Type II DM

Previous PRPC for DM retinopathy

Glaucoma on Bimatoprost

Routine & uncomplicated phaco + PCIOL January 2015

PED a month later
CONTACT DETAILS

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REFERENCES

