Corneal Pathology in Diabetes

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Case Study

- 59 year-old Caucasian male with Type ll 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**

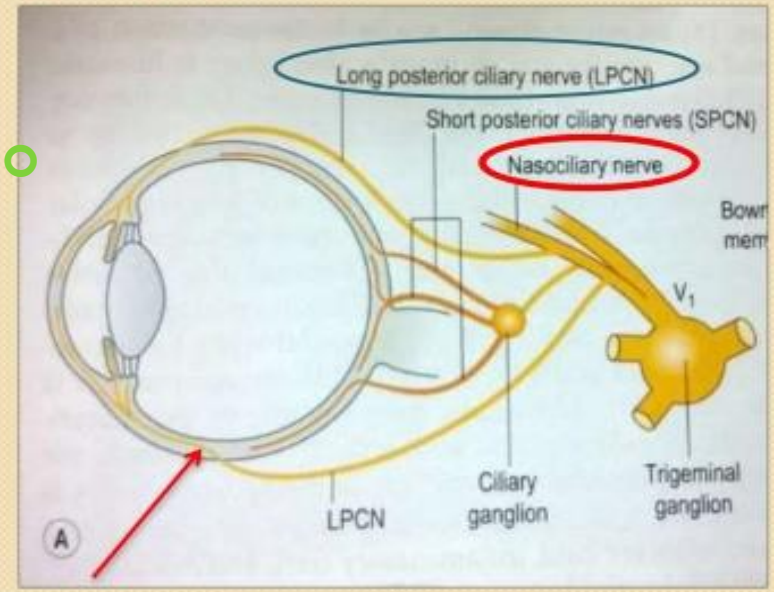
Structural Abnormalities in epithelium/ basement membrane complex

- Lack of Type lV achoring 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

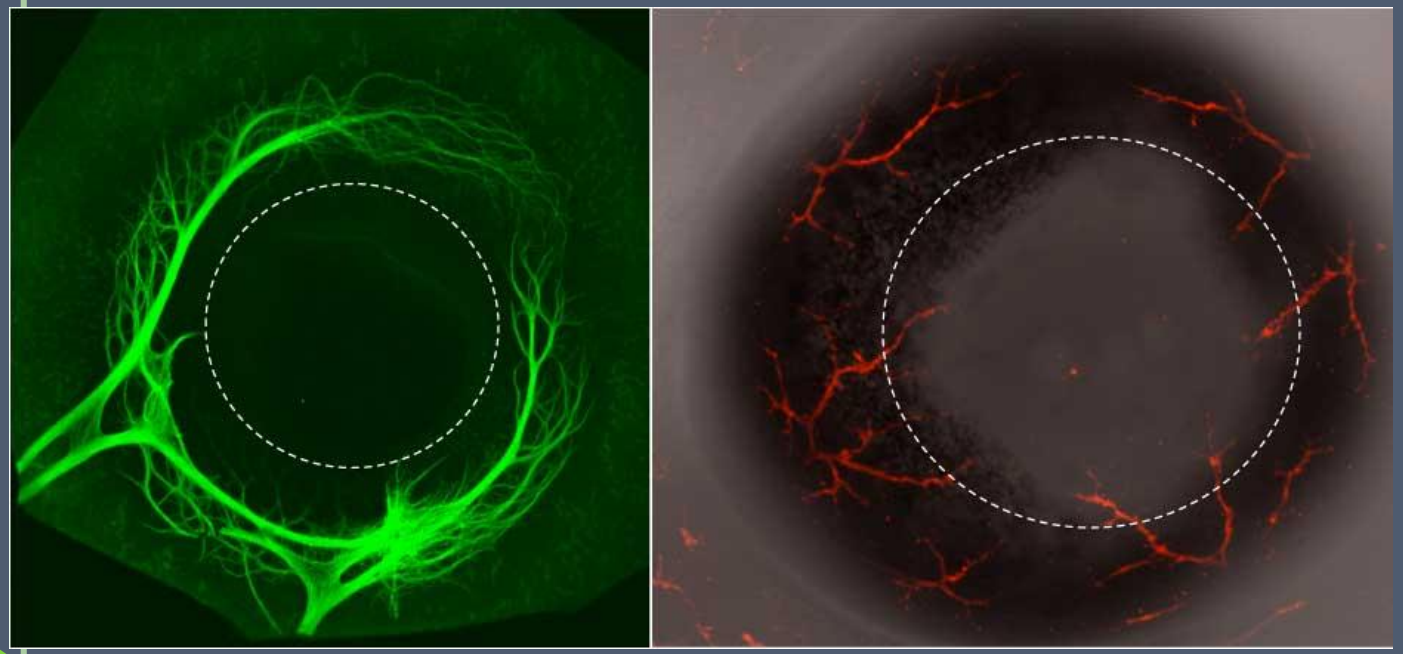
- Cornea is rich in sensory nerve supply derived from ophthalmic division of trigeminal which give branch to;
  - Nasociliary nerve and
  - Ciliary nerves (terminal branch)



- 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

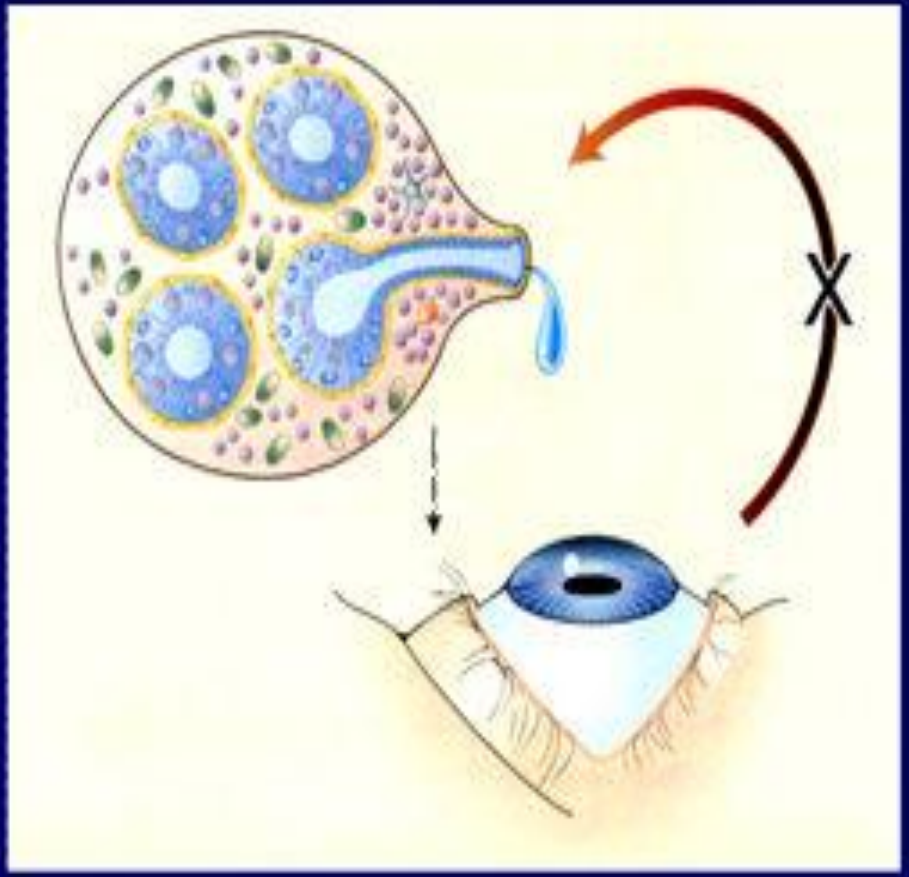
Particularly sensitive along the horizontal meridian and less so along the vertical meridian

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.



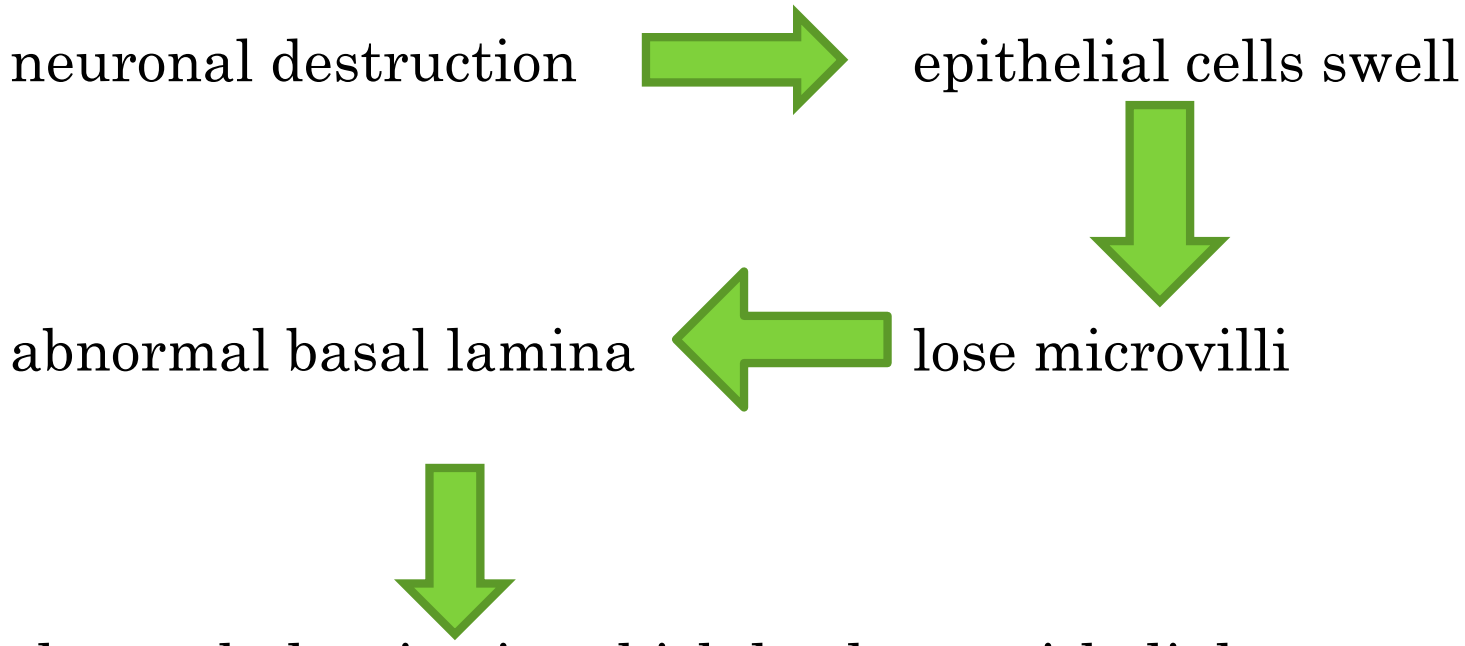
Atlas of Ophthalmology. Bascom Palmer Eye Institute; 2000: 137

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

Corneal Innervation

- Sensory neurons directly influence the integrity of the corneal epithelium.



- 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

Growth Factor	Function
Nerve growth factor (NGF)	Critical for corneal nerve survival and maintenance, axonal branching, elongation, neuronal sprouting, and regeneration
Found in corneal epithelium and stromal keratocytes	
Keratocyte growth factor (KGF)	Stimulates corneal epithelial proliferation, acts specifically on cells of epithelial origin
Expressed in stromal keratocytes	

Neurotrophic Factors in cornea

Growth Factor	Function
Ciliary neurotrophic factor (CNTF)	Promotes corneal epithelial wound healing by activating corneal epithelial stem/progenitor cells
Transforming growth factor-α (TGF-α), interleukin-1β (IL-1β), and platelet-derived growth factor-B (PDGF-B)	Exclusively expressed in the corneal stroma TGF-α and IL-1β can upregulate the transcription of neurotrophins, such as NGF

Corneal sensation

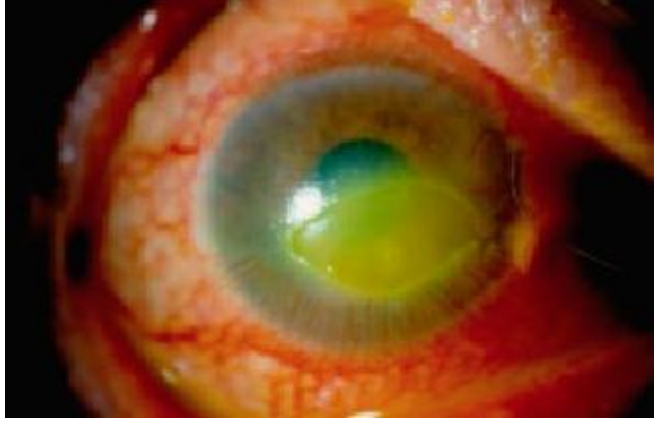
- Decrease in the corneal sensation[23] and loss of nerve derived trophic factor
- insulin-like growth factor 1 (IGF-1) and substance P, a neuropeptide present in sensory nerves, accelerate corneal epithelial wound healing.[24]
- topical application of substance P and IGF-1 accelerated the corneal epithelial 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.

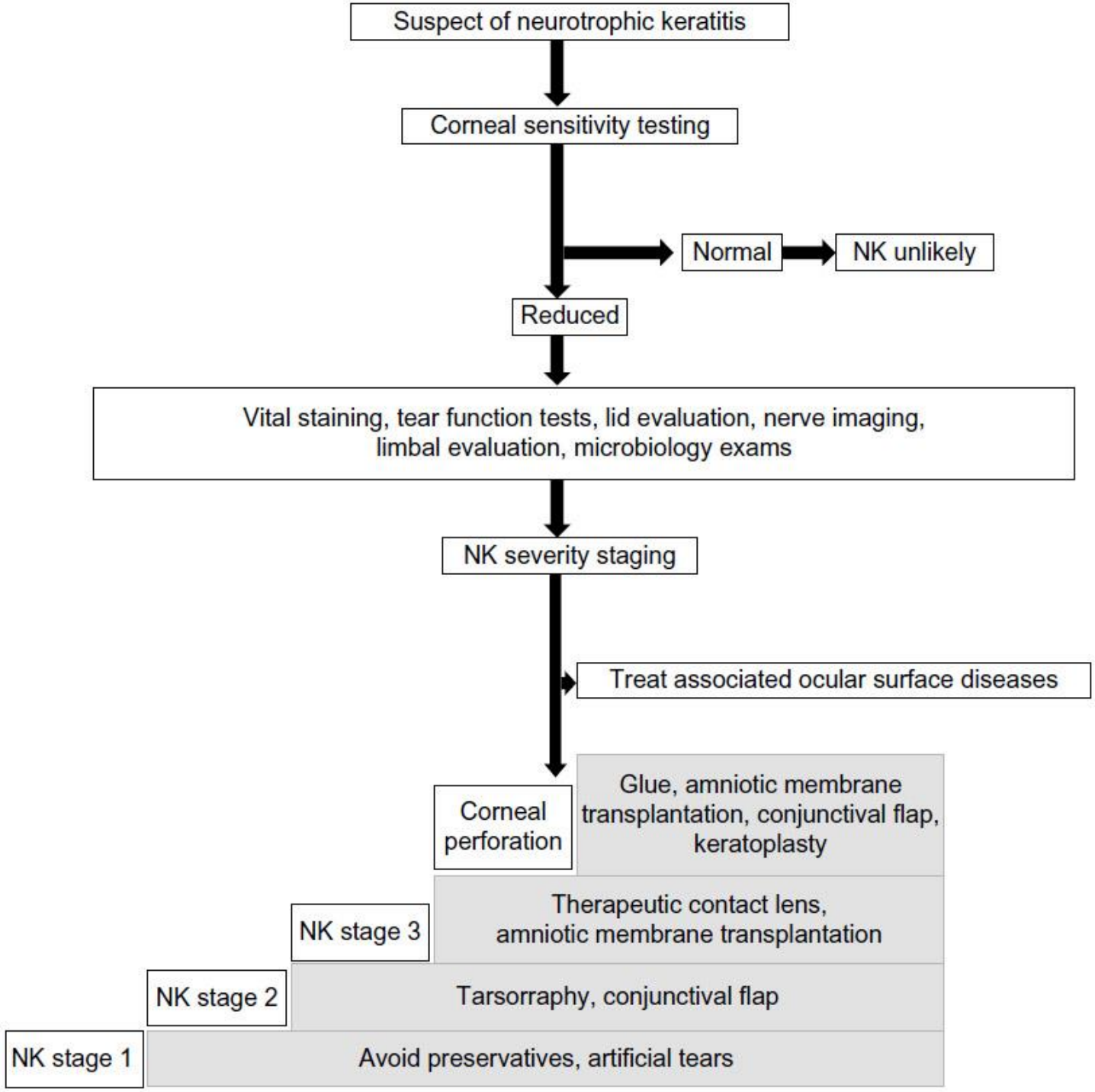
Stage 2



- 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

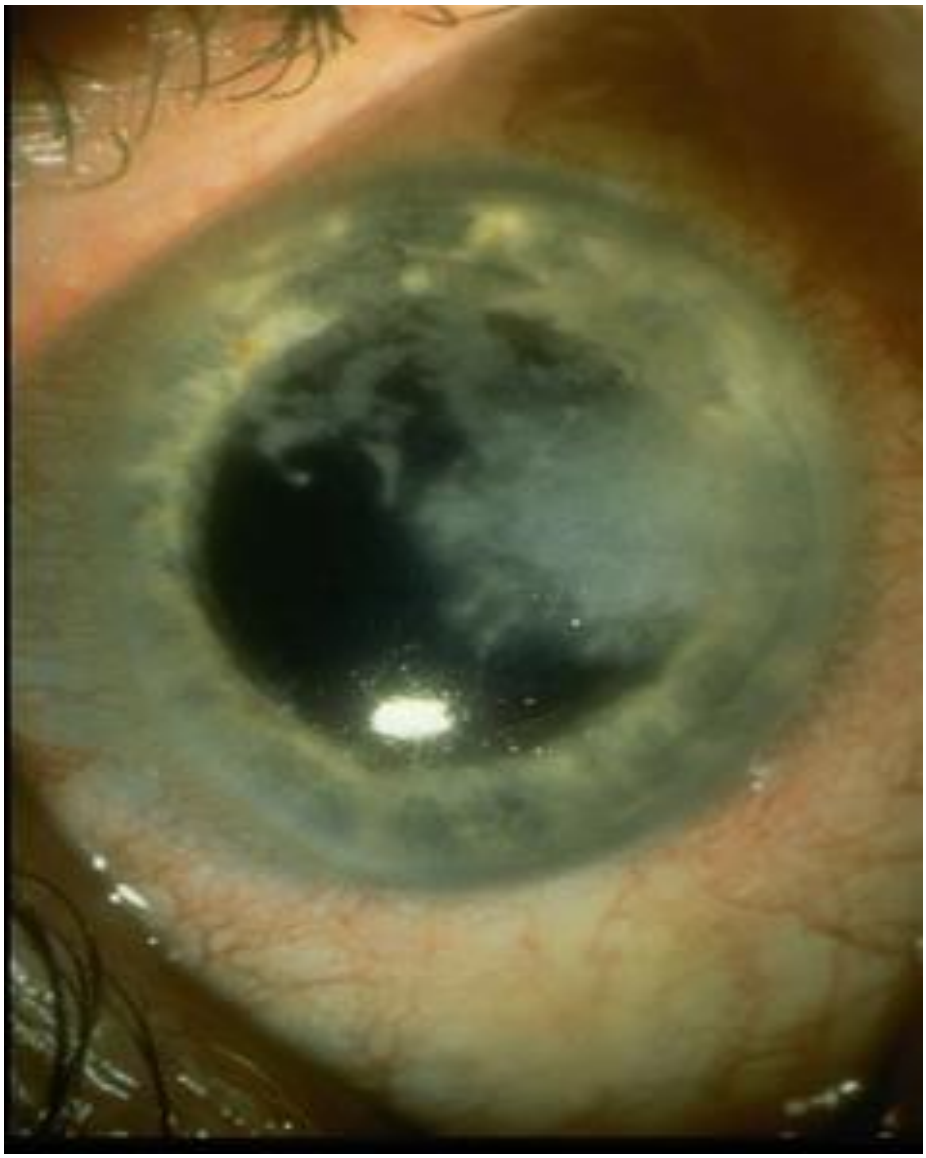
- if stages 1 and 2 are not treated appropriately.
- stromal melting leading to perforation.
- often asymptomatic because of decreased corneal sensation
- immediate attention in order to stop the stromal lysis and prevent perforation.
- topical collagenase inhibitors such as N-acetylcysteine, tetracycline


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
Therapeutic contact lens, amniotic membrane transplantation
NK stage 2
Tarsorraphy, conjunctival flap
NK stage 1
Avoid preservatives, artificial tears

Diabetes & infection risk

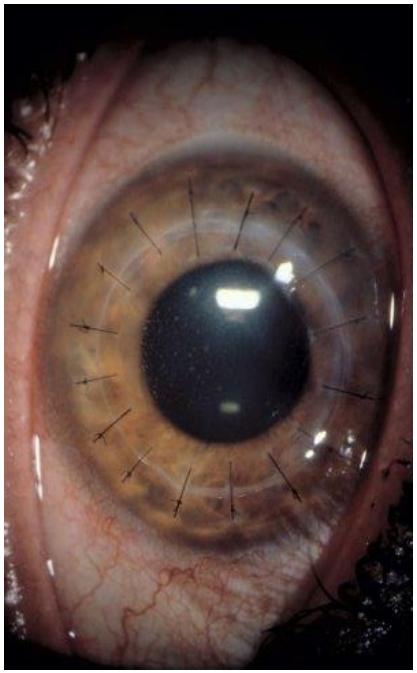
- Impaired neutrophil chemotaxis, phagocytosis and intracellular bacteriacidal activity
  - delayed wound healing
- impaired immune response often exacerbated by vascular insufficiency
- correlated with higher HbA1c levels, longer duration of disease, and the presence of diabetic retinopathy
- weakened barrier - more prone to the development of corneal infections such as fungal keratitis

INFECTIVE FUNGAL KERATITIS



Surgery in diabetic patients

- ……..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

Aldose reductose inhibitors

- 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

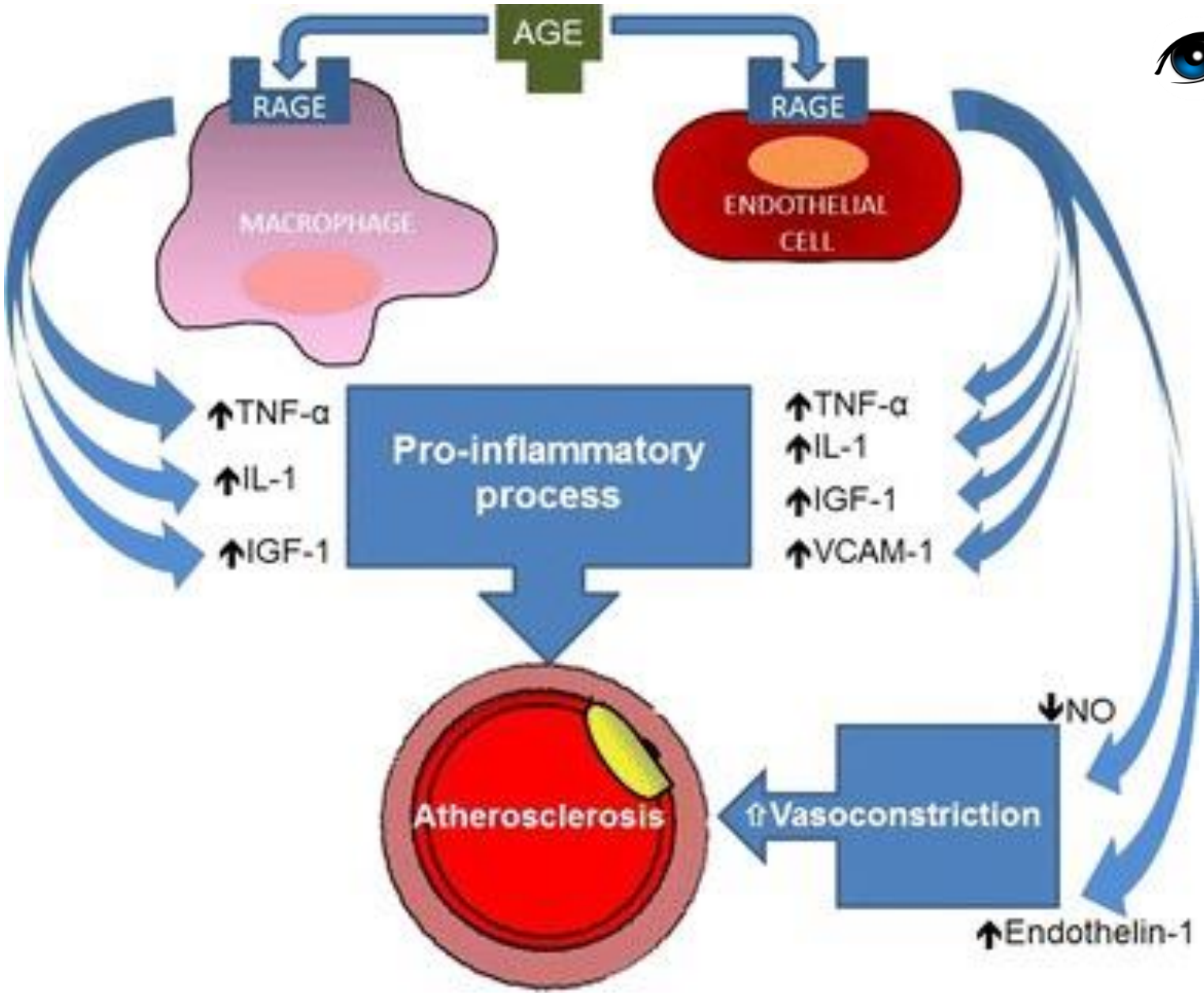
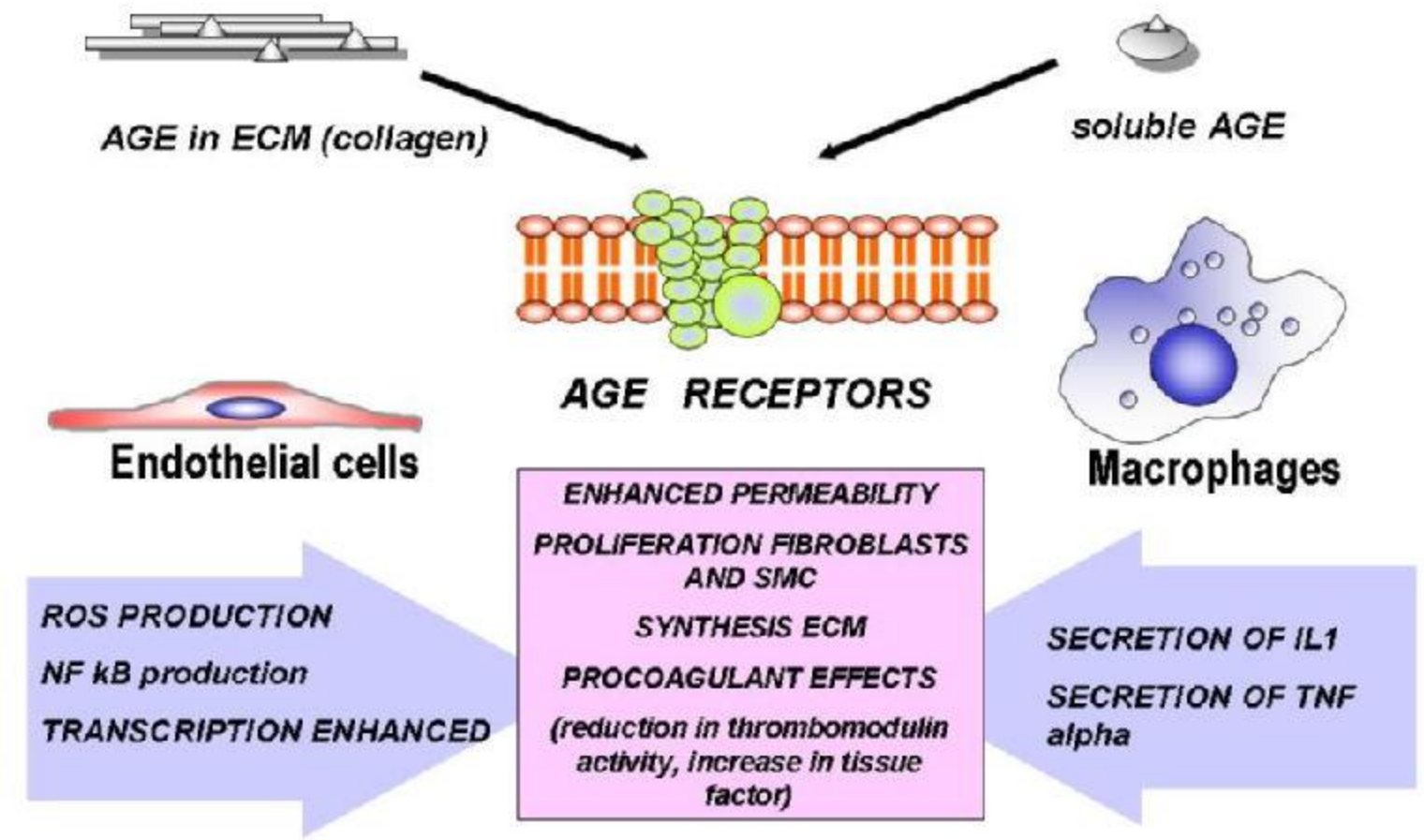

AGE
RAGE
RAGE
MACROPHAGE
ENDOTHELIAL CELL
↑TNF-α
↑IL-1
↑IGF-1
Pro-inflammatory process
↑TNF-α
↑IL-1
↑IGF-1
↑VCAM-1
↓NO
Atherosclerosis
⇧Vasoconstriction
↑Endothelin-1

Fig 5


AGE in ECM (collagen)
soluble AGE
AGE RECEPTORS
Endothelial cells
Macrophages
ENHANCED PERMEABILITY
PROLIFERATION FIBROBLASTS AND SMC
SYNTHESIS ECM
PROCOAGULANT EFFECTS
(reduction in thrombomodulin activity, increase in tissue factor)
ROS PRODUCTION
NF kB production
TRANSCRIPTION ENHANCED
SECRETION OF IL1
SECRETION OF TNF alpha

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 opiod 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

Mechanism of Action	Potential Treatment
Antioxidant	Vitamin C, Vitamin E
Anti-inflammatory	Aspirin
Mitogenic & neurotrophic	NGF, Substance P
Secretagogue	Pilocarpine
Supression of MMP's	Tetracycline
Tear replacement	Autologous serum

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

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