Diabetes and the ocular surface

Insight into the systemic disease

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No Commercial Relationships

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The South Island
Diabetes and the Ocular Surface

1. Diabetes: the systemic disease
2. Neuropathy
3. Corneal neuropathy
4. Ocular surface integrity
Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. Hyperglycaemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels.

- World Health Organisation
Diabetes

Diagnosis

• Fasting venous plasma glucose: ≥7.0mmol/l
• 2 hours after ingestion of 75g oral glucose load: ≥11.1mmol/l

Prevalence

• NZ prevalence: 257,776\(^1\)
• Worldwide: 173 million people\(^2\) and continues to be on the rise\(^3\)

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1. Ministry of Health, 2014
2. WHO, 2002

www.clipartsheep.com
Diabetes classification

• **Type I:**
  - 5-10% of diabetic population
  - Age onset < 30 years
  - Autoimmune destruction and loss of the secretory function of insulin-producing pancreatic β-cells
  - Require insulin

• **Type II:**
  - ~95% of diabetic population
  - Inadequate insulin production / utilisation
  - Risk factors: family hx, overweight, age, ethnicity

• **Impaired glucose tolerance**
Systemic impact of diabetes

- Multi-system disease
  - Premature mortality
  - Macrovascular complications
  - Microvascular complications
    - Retinopathy
      - Retinal capillary damage
      - Progressive capillary occlusion $\rightarrow$ retinal ischaemia $\rightarrow$ new vessels
    - Nephropathy
    - Neuropathy

Diabetic Peripheral Neuropathy

- 60-70% of people with diabetes
- “chronic, symmetrical, length-dependent diabetic sensorimotor polyneuropathy”¹
- Foot ulceration -> 7% of patients ²
  - lower limb amputation, severe pain
  - Significant quality of life costs and financial burden (28K USD at 2 years!)³
- Early and accurate detection


1. Toronto Diabetic Neuropathy Expert Group
Conventional measures of diabetic peripheral neuropathy

Quantitative Sensory Testing (QST)

Nerve conduction testing


Conventional measures of diabetic peripheral neuropathy

Intra-epithelial fiber density measurement in a skin biopsy

- Measures small nerve fiber changes objectively

- BUT... it is invasive and non-repeatable
  - Not appropriate for clinical trials or longitudinal studies

Corneal confocal microscopy

• Only organ where we can directly visualise nerves *in vivo*
• Single points of tissue simultaneously illuminated & imaged in the same plane
• Resulting image very high in resolution\(^1\)
• 500× magnification
• 400 x 400 µm dimension

Corneal nerve structure and function

- Most densely innervated organ in the body\(^1\)
- 100x more sensitive than the conjunctiva\(^1\)
- Derived from the ophthalmic division of the trigeminal nerve


Corneal nerve structure and function

- Nerve bundles enter the cornea at the limbus parallel to the corneal surface
- Penetrate Bowman’s layer to form the corneal subbasal nerve plexus

Corneal confocal microscopy

- Nerve fibre bundle density
- Nerve branch density
- Nerve fibre length
- Nerve fibre width
- Nerve fibre tortuosity
Corneal montage

Diabetes WITH neuropathy

Diabetes WITHOUT neuropathy

Nerve mapping technique originally developed by Patel and McGhee

Corneal montage

Diabetes **WITH** neuropathy

Diabetes **WITHOUT** neuropathy

Corneal confocal microscopy

- Diabetes with neuropathy:
  - Corneal nerve density
  - Corneal nerve length
  - Corneal nerve branch density\(^1,2\)

- Corneal nerve parameters correlate well with nerve fibre loss in skin biopsy\(^1\)

- Can be used to detect and stratify the severity of diabetic peripheral neuropathy

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Predicting diabetic peripheral neuropathy

- Corneal nerve length can predict peripheral neuropathy$^1$
  - 90 px with type 1 diabetes and no DPN
  - Corneal nerve length could predict DPN incidence with 63% sensitivity and 74% specificity

Corneal nerve regeneration - After pancreas and kidney transplantation -

1. Corneal nerve markers are more sensitive
2. Corneal nerves can regenerate

Corneal nerve function

Corneal nerves

- Trophic support to epithelial cells, lacrimal gland, and goblet cells
- Stimulate cell growth, mitosis, differentiation and migration

Epithelial cells

- Trophic support to neurons
- Secrete growth factors
- Promote neurite extension

In diabetes

- Reduction in these mediators
- Disruption in epithelial integrity - ↑ risk of corneal erosions
- Neurotrophic keratopathy

Dry eye in diabetes

- ↑ dry eye signs & symptoms
- ↑ severity with diabetes severity
- ↓ Tear production
- ↓ Tear film stability
- ↓ goblet cell density

Yin et al., Invest Ophthalmol Vis Sci. 2011;52:6589–6596
Neurotrophic keratopathy

- Impaired corneal sensitivity
- Epithelial breakdown
- Delayed wound healing
- Corneal ulceration
- Vision loss
- These signs increase with neuropathic severity, and severity of diabetes

Neurotrophic keratopathy

Yin et al., Invest Ophthalmol Vis Sci. 2011;52:6589–6596
Standard treatment

- Preservative free lubricants
- Minimising evaporation – punctal plugs
- Topical antibiotics
- Bandage CL
- Patching
- Tarsorrhaphy / induced ptosis
Growth Factors

• Insulin-like growth factor-1 (IGF-1)
  – Mediates proliferation and differentiation
• Substance P
  – Neurotransmitter
  – Reduced in eyes with hypoesthesia
• IGF-1 and Substance P
  – *In vitro*: stimulate epithelial migration
  – *In vivo*: effective in treating neurotrophic ulcers\(^1\) and superficial punctate keratitis\(^2\)

Growth Factors

- Nerve Growth Factor
  - Modulates ocular inflammation
  - Corneal epithelial proliferation and differentiation
  - Wound healing promoted\(^1\)
  - No relapse\(^1\)


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Summary

• Expect greater application of the confocal microscopy in both research and clinical settings
• Beware of diabetic ocular surface disease
• Future treatments:
  – NGF
  – IGF & Substance P
• Expect expanded role of optometry in the management of diabetic peripheral neuropathy