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Corneal Confocal Microscopy, a promising new clinical tool for diabetic neuropathy screening.

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Corneal Confocal Microscopy, a promising clinical tool for diabetic neuropathy screening

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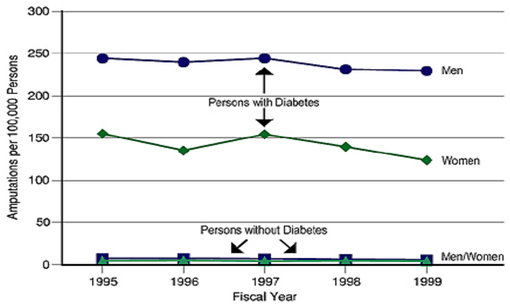
Importance of the Project:

Diabetic neuropathy has major negative impacts on one's morbidity, mortality, and quality of life(Figure 1)[1]. It is highly costly to the healthcare system.

Figure 1. Rates of major amputation in the general Ontario population: 14 fold higher in persons with Diabetes



The lack of an early biomarker for nerve injury of neuropathy in clinical practice impedes the benefit of early identification, early management, prevention of neuropathy-related sequelae, and the accurate evaluation of future therapies in clinical trials. Diabetic Neuropathy begins with small nerve injuries(Figure 3)[4]. The current gold standard test for small nerve injury uses skin biopsies(Figure 2) to examine the morphological changes of intra-epidermal nerve fibres[2,3], a method that is both invasive and costly .

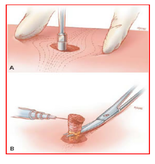
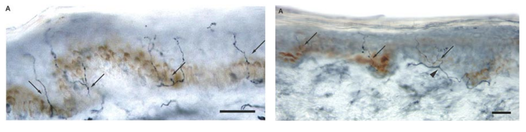


Figure 2. Skin Biopsy



No Neuropathy

Diabetic small-fiber neuropathy

Figure 3. Diabetic Neuropathy begins with small nerve injuries.

Alternatively, morphological examination of the small nerve fibres of the cornea by in-vivo corneal confocal microscopy is a potential early non-invasive method for neuropathy detection(Figure 4)[5]. The corneal nerve fibres are thought to closely represent those that are involved in the length-dependent process of neuropathy. It is therefore important to identify any variables that may influence the corneal nerve morphology, and interfere with its validity as a screening tool of diabetic neuropathy. For example, if there were relationships between corneal nerve fibre length and age, we would need to establish age-stratified thresholds for screening protocols of neuropathy. Although there exists research studying the associations of variables associated with corneal nerve morphology, our study is the first to examine variables specifically associated with corneal nerve fibre length.

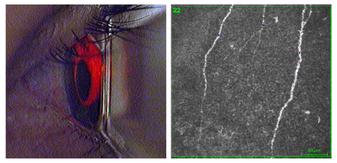
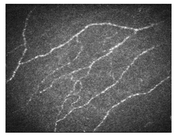


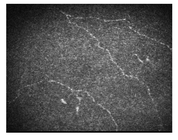
Figure 4. Small nerve fibers in the cornea can be visualized non-invasively with corneal confocal microscopy

Existing State of Knowledge:

Much work has been accomplished regarding the concurrent validity and reproducibility of this technology[6-11]. Corneal nerve fibre length obtained from corneal nerve microscopy has been shown to be highly reproducible and to have a high level of diagnostic validity for the identification of neuropathy. In terms of clinical variables associated with corneal nerve morphology, previous studies have showed conflicting results. Some studies showed that there is no correlation between corneal nerve density and age, others showed increasing age is associated with decreased corneal nerve density. In terms of the effect of contact lens wear on corneal nerve morphology, previous work has suggested that it has no effect. However, the parameters of corneal nerve morphology in this research did not look at nerve fibre length, but rather parameters such as hepatocyte density, nerve fibre width, and nerve fibber density. Our study is the first to examine variables specifically associated with corneal nerve fibre length.



Type 1 Diabetes
No neuropathy



Type 1 Diabetes
Moderate neuropathy

Research Question:

Are there any variables such as age or contact lens wear that may influence corneal nerve fibber length, and thus interfere with its validity as a biomarker of diabetic neuropathy?

Methodology:

We collected clinical variables, electrophysiological exam results, as well as eye history from 64 healthy volunteers. We performed corneal confocal microscopy on these patients, manually traced the nerves on the captured images, and used an image analysis software(CCM Image Analysis tool v1.1 which was provided by Drs R. Malik and M. Dabbah, University of Manchester, Manchester, UK) to determine their corneal nerve fibre length. We then used univariate and multivariate linear regression analysis to determine if there are any variables associated with corneal nerve fibre length.

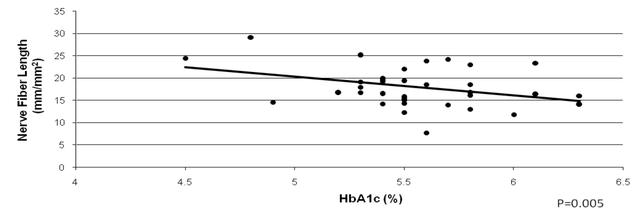
Findings:

Variable	Nerve Fiber Length (mm/mm²) B Value	P Value
HbA1c (%)	-4.511	0.033
Age(yr)	-0.060	0.190
Duration of Contacts Lenswear (yr)	-0.006	0.981

Figure 6. Multivariate Regression Analysis

We found that the corneal nerve fibre length actually is quite variable in healthy volunteers. From the univariate regression analysis, we observed that even though HbA1c(a marker of glycemic control), age and status of contact lens wear were all associated with corneal fibber length. However, HbA1c was the only variable associated with corneal fibre length in the multivariate regression analysis (Figure 6).

Figure 7.Nerve Fiber Length Vs HbA1c



Conclusion:

Since HbA1c is a well-known marker of glycemic control in those living with diabetes, its strong inverse association with corneal nerve fibber length (CNFL) indicates that CNFL is a sensitive measure of nerve damage in non-diabetic individuals. Those who had shorter CNFL tend to have HbA1c in the pre-diabetic range(Figure 7). This helps to support the use of corneal confocal microscopy as a tool to detect early nerve injury.

Acknowledgement

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Reference

1. "Diabetes in Ontario An ICES Practice Atlas." Canadian Diabetes Association, 1 June 2003. Web. 18 Mar. 2015. <http://www.ices.on.ca/~/media/Files/Atlases-Reports/2003/Diabetes-in-Ontario/Full report.ashx>.
2. Tavakoli, Mitra et al. "Corneal Confocal Microscopy: A Novel Means to Detect Nerve Fibre Damage in Idiopathic Small Fibre Neuropathy." *Experimental neurology* 223.1 (2010): 245–250. *PMC*. Web. 18 Mar. 2015.
3. "Skin Biopsy." *ProcGuide:*. Web. 18 Mar. 2015. http://www.anwresidency.com/simulation/guide/skinbx.html.
4. Lauria, Giuseppe, and Grazia Devigili. "Skin Biopsy as a Diagnostic Tool in Peripheral Neuropathy." *Nature.com*. Nature Publishing Group, 1 July 2007. Web. 18 Mar. 2015. <http://www.nature.com/nrneurol/journal/v3/n10/full/ncpneuro0630.html>."HRT3 - Heidelberg Retina Tomograph." *HRT3 - Heidelberg Retina Tomograph*. Web. 18 Mar. 2015. http://www.optech.net.au/optech_net_004.htm.
5. Hossain P, Sachdev A, Malik RA. Early detection of diabetic peripheral neuropathy with corneal confocal microscopy. Lancet 2005; 366: 1340–1343.
6. Malik RA, Kallinikos P, Abbott CA, van Schie CH, Morgan P, Efron N et al. Corneal confocal microscopy: a non-invasive surrogate of nerve fibre damage and repair in diabetic patients. Diabetologia 2003; 46(5): 683–688.
7. Patel DV, Tavakoli M, Craig JP, Efron N, McGhee CN. Corneal sensitivity and slit scanning in vivo confocal microscopy of the subbasal nerve plexus of the normal central and peripheral human cornea. Cornea 2009; 28: 735–740.
8. Oliveira-Soto L, Efron N. Morphology of corneal nerves in soft contact lens wear. A comparative study using confocal microscopy. Ophthalmic Physiol Opt 2003; 23: 163–174.
9. Efron N, Mutalib HA, Perez-Gomez I, Koh HH. Confocal micro- scopic observations of the human cornea following overnight con- tact lens wear. Clin Exp Optom 2002; 85: 149–155.
10. Efron N, Perez-Gomez I, Morgan PB. Confocal microscopic observations of stromal keratocytes during extended contact lens wear. Clin Exp Optom 2002; 85: 156–160.