Functional and structural deficits in preclinical and early diabetic retinopathy point to diabetic retinal neuropathy

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Introduction

Increasing evidence shows that diabetic retinopathy (DR) is not only a microvascular but also a neurodegenerative disease.[1,2] Many studies of diabetic retinal neurodegeneration (DRN) only examined the ganglion cell complex (GCC).[3,4] As far as we are aware, this is the first longitudinal study that compared the macular function and structure of healthy participants (HP) with participants with diabetes (PWD) using the handheld radial shape discrimination (hRSD) test and evaluated retinal thickness of all layers in early DR.

Methods

Participants

- Group 1: 50 HP (55±14y, 26 males)
- Group 2: 26 PWD with no DR (ETDRS grade 10; 55±14y, 14 males)
- Group 3: 46 PWD with early DR (ETDRS grade 20/35; 57±17y, 23 males)

Procedures

- Macular function was measured using myVisionTrack (mVT) application deployed on an Apple iPod Touch and following a previously published protocol[5] and distance and near visual acuity (VA).
- Macular structure was assessed using Heidelberg Spectralis optical coherence tomography (OCT) (Figure 1). Total retinal thickness and the thickness of individual layers in the Early Treatment Diabetic Retinopathy Study (ETDRS) subfields (central, inner ring, outer ring) were examined.

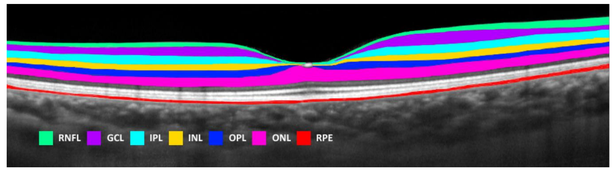


Figure 1. Example Heidelberg Spectralis output of segmented retinal layers from a healthy participant.

Longitudinal data

- Available for 23 PWD who had a follow-up after 205±109 days.

Results

Macular Function

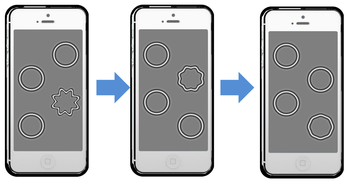


Figure 2. The 4AFC hRSD test

- In PWD with no or early DR, there was a decline in visual function compared to HP (Figures 2 and 3).
- hRSD threshold, distance and near VA were generally worse with increasing disease severity
- These declines were statistically significant

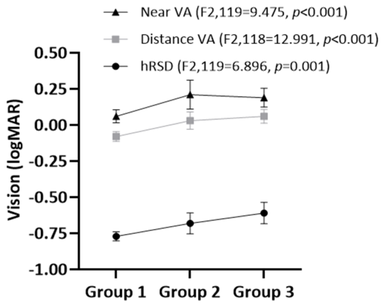


Figure 3. Mean (±95%CI) hRSD threshold, distance and near VA of all groups tested with ANOVA.

Macular Structure

Total Retinal thickness by ETDRS subfields

- Compared to Group 1, mean total retinal thicknesses were significantly reduced in Groups 2 and 3 across all 9 subfields (range -2.7 to -4.9%; all $p<0.05$) (Figure 3) except for Group 2 in the central subfield (Figure 4).

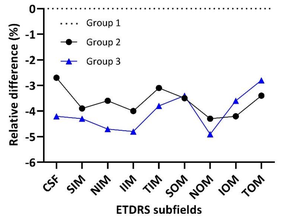


Figure 4. Relative difference* (RD; %) of mean total retinal thickness between groups in all ETDRS subfields.

*RD calculated as the difference between the mean retinal thickness of PWD and Group 1 divided by the retinal thickness of Group 1, expressed as a percentage.

Differential effect on retinal layers

- Compared to Group 1, Groups 2 and 3 had thinning in all inner retinal layers across all subfields (RNFL, -0.8 to -12.3%; GCL, -4.6 to -9.9%; IPL, -4.0 to -9.0%) except for INL in the central subfield (Figure 5).
- These findings were statistically significant for RNFL in the outer ring (all $p<0.05$) and GCL and IPL in the inner ring (all p<0.01).
- For Group 3 this was also significant for GCL in the outer ring ($p=0.015$).
- In the outer retina layers, compared to Group 1 there was thinning of the ONL in Groups 2 and 3 in all subfields (-5.1 to -9.7%) and this was significant in the central subfield (all $p<0.05$).

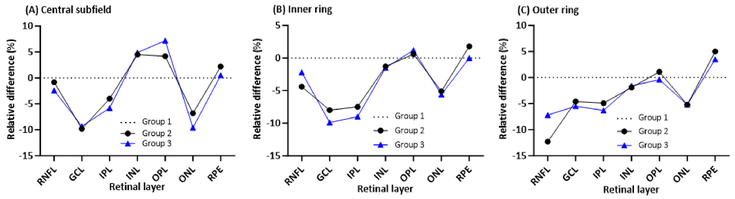


Figure 5. Relative difference (RD; %) of different retinal layers between groups in the central subfield (A), inner ring (B) and outer ring (C).

Longitudinal data

- No change in macular function
- Decrease in GCL, IPL and INL (all $p<0.05$).

Discussion

Functional and structural changes in this study are consistent with DRN. Longitudinal results showed increasing thinning of the inner retinal layers supporting DRN as a progressive condition (Figure 6).

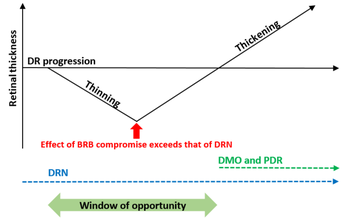


Figure 6. As DR progresses (horizontal axis), retinal thinning as detected by OCT (vertical axis) can occur in DRN. When the effects of the blood-retinal-barrier (BRB) compromise on the retina exceed that of DRN (red arrow), retinal thickness starts to increase. With the increasing compromise of the BRB, diabetic macular oedema (DMO) and proliferative diabetic retinopathy (PDR) can become apparent leading to retinal thickening. The window of opportunity for neuroprotective agents to work in DRN should be prior to the onset of DMO and PDR.

Conclusion

Functional and structural changes are detectable in early DR, consistent with DRN. It is important to explore potential neuroprotective agents to manage DRN.

References

1. van de Kreeke, J. A., Darma, S., Chan Pin Yin, J., et al. (2020) 'The spatial relation of diabetic retinal neurodegeneration with diabetic retinopathy', *PLoS One*, 15(4), pp. e0231552.
2. Sohn, E. H., van Dijk, H. W., Jiao, C., et al. (2016) 'Retinal neurodegeneration may precede microvascular changes characteristic of diabetic retinopathy in diabetes mellitus', Proc Natl Acad Sci U S A, 113(19), pp. E2655-64.
3. Rodrigues, E. B., Urias, M. G., Penha, F. M., et al. (2015) 'Diabetes induces changes in neuroretina before retinal vessels: a spectral-domain optical coherence tomography study', *Int J Retina Vitreous*, 1, pp. 4.
4. Vujosevic, S. and Midena, E. (2013) 'Retinal Layers Changes in Human Preclinical and Early Clinical Diabetic Retinopathy Support Early Retinal Neuronal and Müller Cells Alterations', *J Diabetes Res*, 2013, pp. 905058.
5. Ku, J., Milling, A., Pitrelli Vazquez, N., et al. (2016) 'Performance, usability and comparison of two versions of a new macular vision test: the handheld Radial Shape Discrimination test', *PeerJ*, 4, pp. e2650.

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