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EXTENDED ABSTRACT

A10 Progression of Ganglion Cell-Inner Plexiform layer thickness in the initial stages of diabetic retinopathy in type 2 diabetic patients: a 5-year longitudinal study

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Introduction

Diabetic Retinopathy (DR) is a frequent complication of Diabetes Mellitus (DM) and the main cause of vision loss in the working population in western countries. Diabetic Retinopathy has always been considered a microvascular disease, but it has been suggested that neurodegeneration is also associated with this complex pathology[1], although there is evidence indicating that the neurodegenerative process may progress independently[2]. To evaluate this potential association, we have examined the progression of neurodegeneration over a 5-year period of follow-up (considering thinning of ganglion cell + inner plexiform retinal layers (GCL+IPL) in individuals with type 2 diabetes (T2D) and nonproliferative DR) and explored whether it is associated with microaneurysm turnover (MAT), disease level at baseline and severity progression.

Methods

This study was designed as a 5-year prospective, longitudinal study (ClinicalTrials.gov identifier: NCT03010397), to evaluate disease progression in T2D individuals.

212 T2D individuals with mild non-proliferative diabetic retinopathy (NPDR, ETDRS (Early Treatment Diabetic Retinopathy Study) level 20 or 35)[3] were included in the study, of which 145 completed the 5-year follow-up, with ophthalmological examinations performed at baseline and annually (one eye per patient). GCL+IPL average thickness was evaluated by optical coherence tomography (OCT). Classification in ETDRS levels assesses severity of DR and was performed by grading of 7-fields color fundus photography. Severity progression was determined as step changes between levels of ETDRS at baseline and at the 5-year follow-up and was classified as improvement/maintenance or worsening. Microaneurysm turnover (MAT) was evaluated using the RetMarkerDR considering a cut-off of 6, identified previously to characterize microvascular disease activity [4].

Linear mixed-effects models with a random intercept for the patient were used to assess the progression of GCL+IPL thickness over time (6 annual visits), adjusting for age and gender. Separate models were used to analyse the effect of ETDRS severity progression, ETDRS at baseline, MAT≥6 and the interaction of these parameters with time on GCL+IPL thickness. Statistical analysis was performed with Stata 16.1 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.Stata Corp. LP, College Station, TX, USA), and a P -value ≤0.05 was considered statistically significant.

Results

The analysis included 144 subjects, as one individual was excluded due to inconsistencies in the automatically collected OCT data.

The effect estimates of time, adjusted for age and gender, on GCL+IPL average thickness are reported in table 1 and expected progression of GCL+IPL thickness over the 6 visits is depicted in figure 1. GCL+IPL thickness showed an estimated decrease of 1.40µm over the 5-year period in relation to the first visit, when other variables remain constant, adjusted for age (p-value: <0.001) and gender (p-value: 0.015).

When evaluating the effect of the variables of interest, by adding them to the model, the effect of ETDRS step change was not statistically significant (p-value: 0.332), but the interaction of ETDRS level progression with time showed a significant effect on GCL+IPL average thickness (p-value: 0.008) (figure 2). Noteworthy, the effect of time on ETDRS step change groups was significant on those individuals

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Supplementary material:
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Conflict of interest:
D.T., M.H.M, I.P.M., T.S, A.R.S and C.L. declare no conflict of interests. J.C.-V. reports grants from Carl Zeiss Meditec and is consultant for Alimera Sciences, Allergan, Bayer, Gene Signal, Novartis, Pfizer, Precision Ocular Ltd., Roche, Sanofi-Aventis, Vifor Pharma, and Carl Zeiss Meditec.

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where DR severity was maintained or improved (p-value: <0.001), and not in those that showed ETDRS severity worsening (p-value: 0.079), suggesting that GCL+IPL decrease does not appear to be associated with DR severity progression.

Finally, the models that considered ETDRS level at baseline and MAT did not show significant effect of these parameters (p-value: 0.821 and p-value: 0.682, respectively) and their interaction with time (p-value: 0.971 and p-value: 0.992, respectively) on GCL+IPL average thickness (figure 3, Supplementary Material).

Table 1 - Fixed effects ß coefficients (µm), 95% Confidence Interval (CI) and p-value of age, gender, and time on GCL+IPL Average thickness obtained from linear mixed effects model with a random intercept for patient.

Fixed Effects	ß	95% CI		p-value
		Lower	Upper	
Age	-0.30	-0.46	-0.14	<0.001
Gender				
Female	3.07	0.60	5.54	0.015
Time				
Visit 2	-0.75	-1.10	-0.41	<0.001
Visit 3	-0.59	-0.94	-0.25	0.001
Visit 4	-0.82	-1.17	-0.47	<0.001
Visit 5	-1.29	-1.64	-0.95	<0.001
Visit 6	-1.40	-1.74	-1.06	<0.001
Intercept	98.4	87.9	109.0	<0.001

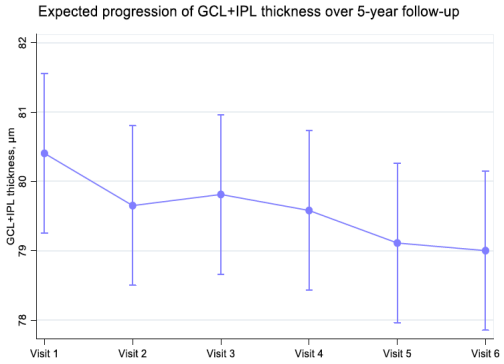

Figure 1 - Expected progression of GCL+IPL thickness over 5 years period by ETDRS step change: predictive margins of the interaction of time with ETDRS step change, with 95% CI (p-value of the interaction: 0.008)

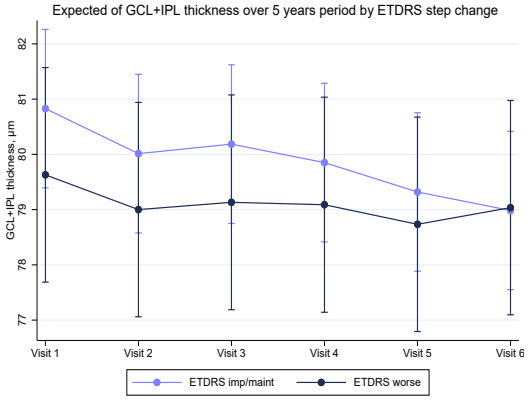

Figure 2 - Expect progression of GCL+IPL thickness (*µm*) over 5-year follow-up: predictive margins of time with 95% CI, adjusted for age and gender obtained from linear mixed effects model with a random intercept for the patient.

Discussion and Conclusions

Through these analyses, we have demonstrated that in a 5-year period of follow-up there is progressive thinning of GCL+IPL, indicating that progressive neurodegeneration occurs in NPDR. However, no clear association was identified with microvascular disease (represented by MAT), disease level and severity progression of the retinal disease. Future studies should further explore the association of severity improvement and maintenance with neurodegenerative changes.

Ethics committee and informed consent:

The current research was approved by an independent ethics committee and subjects gave their informed consent before they were enrolled in the study.

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