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Association of Predominantly Peripheral Lesions on Ultrawide Field Imaging and the Risk of Diabetic Retinopathy Worsening Over Time: Results from the DRCR Retina Network Protocol AA

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DESIGN OF STUDY. Prospective multicenter longitudinal observational study
PURPOSE. To determine whether predominantly peripheral lesions (PPL) identified on UWF imaging and angiographic risk factors are associated with increased disease worsening beyond the risk associated with baseline ETDRS DR severity score (DRSS).
METHODS. A total 544 study eyes with nonproliferative DR (NPDR) from 367 adult participants with diabetes. 200° UWF-colour images were collected at each annual visit through 4 years. UWF-fluorescein angiography (FA) images imaging was performed at baseline, 1 and 4 years. A centralized reading center graded DR severity and PPL on UWF-colour (colour-PPL) and UWF-FA (FA-PPL). PPL were defined as DR lesions with a greater extent outside versus inside the standard ETDRS fields. Initiation of treatment for DR and/or DME was at investigator discretion. The primary outcome was disease worsening over 4 years, defined as 2 or more steps DRSS worsening within ETDRS fields on UWF-colour images or receipt of DR treatment.
RESULTS. The 4-year disease worsening rates were 45% for eyes with mild NPDR at baseline, 40% for moderate NPDR, 26% for moderately-severe NPDR, and 43% for severe NPDR. At baseline, 41% of eyes had colour-PPL and 46% had FA-PPL. Disease worsening was not associated with baseline colour-PPL (present vs absent: 38% vs 43%; HR, 0.78; 95% CI, 0.57–1.08; $p = 0.13$) but was associated with baseline FA-PPL (present vs absent: 50% vs 31%; HR, 1.72; 95% CI, 1.25–2.36; $p < 0.001$).
CONCLUSIONS. Although no relationship was identified with colour-PPL, presence of FA-PPL was associated with greater risk of disease worsening over 4 years, independent of baseline DR severity level. These results suggest that evaluation of the retinal far periphery is important in understanding which eyes with NPDR are at higher risk for future disease worsening. Peripheral findings on UWF-FA should be considered for incorporation in future DR staging systems.

Characterization of Two-Year Progression of Neurodegeneration in Different Risk Phenotypes of Diabetic Retinopathy

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DESIGN. Prospective observational 2-year study.
PURPOSE. To characterize the two-year progression of neurodegeneration in different diabetic retinopathy (DR) risk phenotypes in type 2 diabetes.
METHODS. A prospective longitudinal cohort study (CORDIS, NCT03696810) was conducted with 3 visits (baseline, 6-months and one-year). Demographic and systemic data included age, sex, diabetes duration, lipid profile and haemoglobin A1c (HbA1c). Ophthalmological examinations included visual acuity (BCVA), colour fundus photography (CFP) and optical coherence tomography (OCT and OCTA). Phenotype classification was performed, at 6-month visit, based on microaneurysm turnover (MAT on CFP) and central retinal thickness (CRT, on OCT). Only risk phenotypes B (MAT < 6 and increased CRT) and C (MAT ≥ 6 with or without increased CRT) were

included. ETDRS grading was performed at the baseline and last visit based on 7-fields CFP.

RESULTS. Of the 133 T2D individuals included in the study, 81 (60%) eyes were classified as phenotype B and 52 (40%) eyes as phenotype C. Of these, 127 completed the two-year follow-up, with 24 (19%) developing centre involving macular edema (CIME) and 2 (1.6%) clinically significant macular edema (CSME).

Neurodegeneration represented by thinning of the GCL +IPL was present in both phenotypes showing no statistically significant differences between these phenotypes. Furthermore, GCL+IPL thickness decreased with time (average of -0.605 µm/year; $p = 0.010$). This decrease remained statistically significant ($ß = 0.624$, $p = 0.006$) when controlling for age, sex, diabetes duration and HbA1c. Changes in time for GCL+IPL thickness are also negatively associated with longitudinal changes in FAZ area ($\beta = -1.469$), FAZ perimeter and deep capillary plexus vessel density in phenotype C and in contrast with Phenotype B. No correlation was found between the presence of increased neurodegeneration and the development of CIME.

CONCLUSIONS. In the two-year period of follow-up both phenotypes B and C showed progression in retinal neurodegenerative changes in phenotype C. The neurodegeneration is associated with microvascular related variables indicative of capillary closure. There is no association between the progression in neurodegeneration and development of CIME.

Transcriptomic Analysis Reveals that Retinal Neuromodulation is the Main Underlying Mechanisms of the Neuroprotective Effect of Sitagliptin in Diabetic Retina

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DESIGN. Neurovascular unit (NVU) impairment is an early event in the pathogenesis of diabetic retinopathy (DR), which participates in the neurodegeneration and the early microvascular impairment of the diabetic retina. Consequently, NVU becomes an emergent therapeutic target of DR. The diminishment of synaptic protein expression, the impairment of neurotransmission and alterations in neuronal morphology have been described as underlying mechanisms of NVU impairment. Topical administration (eye drops) of sitagliptin, dipeptidyl peptidase-4 inhibitor (DPP-4i), prevented retinal neurodegeneration induced by diabetes in db/db mice.

PURPOSE. To further explore the mechanisms involved in the beneficial effects of DPP-4i on diabetes-induced retinal neurodegeneration, we have compared the retinal expression patterns of vehicle-treated db/db mice (an experimental model of DR) with db/db mice treated with sitagliptin.

METHODS. Ten db/db mice, aged 10 weeks, were topically treated with sitagliptin eye drops (5 µL/eye; concentration: 10 mg/mL) for 2 weeks twice per day, while other ten db/db were received a topical administration of vehicle (5 µL/eye). Ten db/+ mice (non-diabetic mice) were assigned as control group. At 12 weeks, after euthanasia, one eye was used for a transcriptomic analysis and the other for its validation through RT-PCR and for protein assays through Western Blotting (WB) and Immunohistochemistry (IHC). Full-field electroretinogram recordings were used to address retinal functionality.

RESULTS. Diabetic mice topically treated with sitagliptin presented different expression patterns in the retina in comparison to those treated with vehicle. In the analysis of biological significance, neurotransmission was the most enriched biological process. Additionally, we observed that both mRNA and WB/IHC of presynaptic proteins involved in vesicle biogenesis, mobilization, docking, fusion and recycling, were down-regulated in db/db mice retinas in comparison with non-diabetic controls. Topical administration of sitagliptin inhibits this down-regulation caused by diabetes and improves the functionality of diabetic retinas. This effect was unrelated to blood glucose improvement.

CONCLUSIONS. Sitagliptin exerts neuroprotective effects in db/db mice retinas by inhibiting the diabetes-induced down-regulation of key presynaptic proteins. This finding open up a new strategy for treating not only DR but also other retinal diseases in which synaptic abnormalities/neurodegeneration play a crucial role.

Inflammation is Underlying in Retinal Degenerations: Similarities and Differences Between Diabetic Retinopathy and Retinal Degeneration in Huntington's Disease

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