Examining whether growth differentiation factor-15 is altered in the early stages of diabetic retinopathy in individuals with type 2 diabetes

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Circulating levels of growth differentiation factor-15 (GDF-15), a member of the transforming growth factor-β superfamily, are associated with insulin resistance, incidence of diabetes, kidney function and metformin use. Furthermore, it has been shown to be altered with increasing diabetic retinopathy severity in Asian individuals with type 2 diabetes. The aim of this research is to examine whether GDF-15 is altered in the early stages of diabetic retinopathy in type 2 diabetes.

Methods: Participants with type 2 diabetes and either no or early diabetic retinopathy with GDF-15 measurements were selected from the Exeter SUMMIT Diabetic Retinopathy cohort. Diabetic retinopathy was graded from fundus photography in line with the English Diabetic Retinopathy Grading scheme. Early retinopathy was defined as background retinopathy (R1). Circulating GDF-15 was analysed by the Proximity Extension Assay (PEA) technique using the Proseek Multiplex CVD96×96 reagents kit (Olink Bioscience, Uppsala), data are presented as arbitrary units.

Results: 214 Caucasian individuals with type 2 diabetes were selected, 117 and 97 in the no DR and early DR groups, respectively. There was no difference in age, HbA1c, estimated glomerular filtration rate (eGFR) between groups. Duration of diabetes was longer and urinary albumin-creatinine ratio (ACR) higher in the early DR group compared to the no DR Group. 71% and 81% of the no DR and early DR group were taking metformin, respectively. GDF-15 levels were significantly higher in the early DR compared to no DR group (No DR: mean (SD): 9.98(0.73) vs Early DR 10.33(0.81), $p < 0.001$ t-test). The difference in GDF-15 remained when adjusted for age, eGFR, HbA1c, ACR, duration of diabetes and presence of CVD (unstandardised beta (standard error): 0.205(0.101), standardised beta: 0.130, $p=0.043$), but was lost when further adjusted for metformin use (0.162(0.096), 0.103, $p=0.092$).

Conclusion: Circulating GDF-15 levels are increased in early DR in individuals with type 2 diabetes, however, this increase, at least in part, may be explained by the higher proportion of patients on metformin in the early DR group compared to the no DR group.