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Association between Vascular Density and Loss of Protective RAS during Early NPDR by Fractal Dimension

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PURPOSE

Our hypothesis predicts that blood vessels within the retina increase in density during early-stage nonproliferative diabetic retinopathy (NPDR), based on previous results of a small retrospective study.[1] For the current prospective study, the remodeling of arteries and veins during progression of early NPDR is assessed by a repertoire of parameters that includes the fractal dimension (D_f). In complex structures such as branching vascular trees, D_f is a sensitive measure of space-filing capacity.[1,2] The renin-angiotensin system (RAS) is implicated in DR pathogenesis and the function of circulating angiogenic cells (CACs), a critical bone marrow-derived population instrumental in vascular repair.[3–6]

METHODS

Arterial and venous branching patterns were extracted from images of 6 normal controls and 3 early NPDR subjects (2 moderate, 1 mild) acquired by Heidelberg Spectralis® OCT following fluorescein angiography (FA). The vascular branching patterns were analyzed by NASA's VESsel GENeration Analysis (VESGEN) software, in which skeletonized representations were generated automatically to yield D_f by the box-counting method.[2] For binary 2D images, D_f varies between limiting Euclidean dimensions of 1 and 2. Peripheral blood of diabetics and controls was collected for CD34+ CAC isolation. The gene expression of RAS in CACs was assessed by qPCR for Mas receptor to Ang-(1-7). The vasoreparative function of the CACs was measured by migration ability toward CXCL12 (SDF-1).

RESULTS

By D_f, venous and arterial densities were 1.370 ± 0.006 and 1.329 ± 0.016 for early NPDR, compared to 1.318 ± 0.012 and 1.320 ± 0.036 for control. The space filling capacity in early NPDR measured by D_f, a sensitive parameter, therefore demonstrated a pronounced increase for veins, but not for arteries. Mas receptor mRNA in CACs was increased in diabetics without DR but reduced with onset of NPDR, indicating possible loss of compensation of protective RAS during early DR. Migratory dysfunction of CD34+ cells was further associated with DR.

CONCLUSIONS

As assessed by the fractal dimension in our preliminary study, the space-filling capacity of veins, but not arteries, was greater in early NPDR than in control. Larger patient populations will be examined as we complete our ongoing longitudinal study. Results further suggest the protective RAS axis within diabetic CACs is lost early in DR and is associated with increased vascular remodeling as evidenced by VESGEN analysis.

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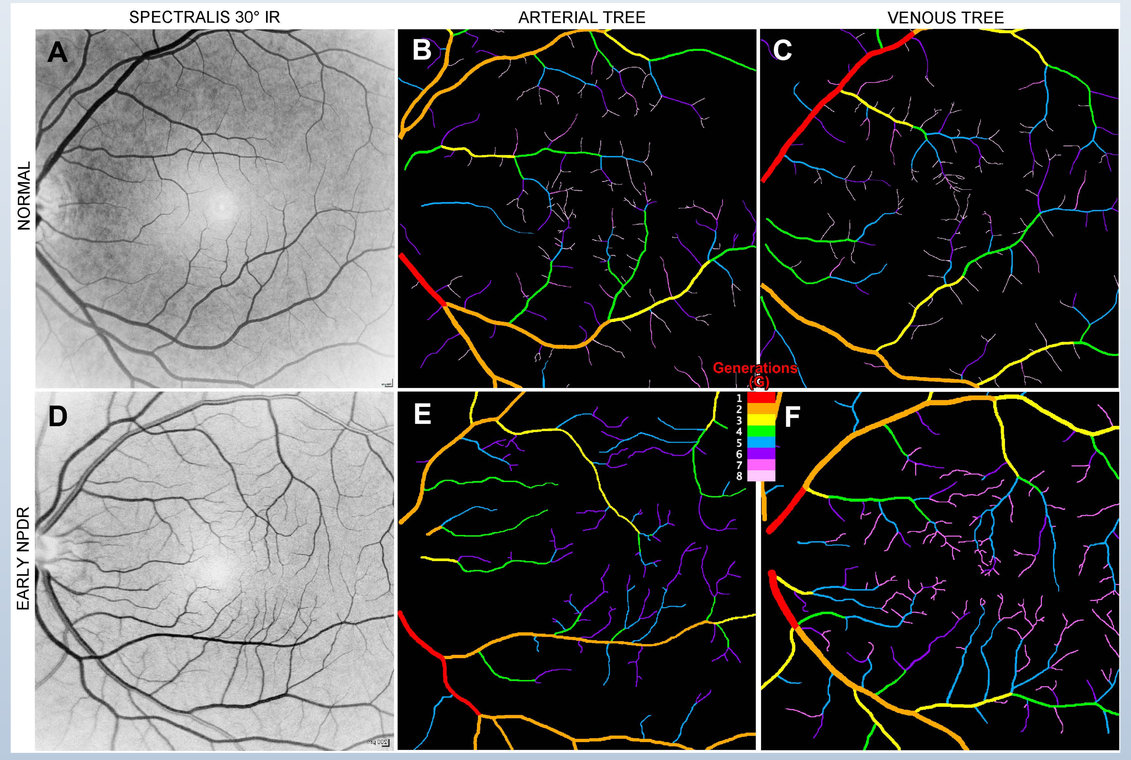

Figure 1 Increased Venous Density in Early-Stage NPDR by Fractal Dimension

Results are illustrated with representative 30 degree Spectralis® fluorescein images and VESGEN vascular maps. From comparison of normal subjects to early NPDR (*A,D*), arterial density by D_f did not differ significantly (*B,E*). Venous density, however, increased in early NPDR (*C,F*). Branching generations (pseudo-colored per legend for Branching Generations, G_1-G_8) were automatically mapped by VESGEN according to physiological vascular branching rules and quantified by parameters (Results) such as D_f reported here.

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