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

Krishnan Radhakrishnan1,2, Ruchi J. Vyas3, Murray, Matthew3, Marina Predovic3, Shiyin Lim3, Douglas Bryant4, Yaqian Duan3, Maria B. Grant4,5, K. V. Chalam6, Patricia Parsons-Wingerter3

1Clinical Epidemiology Research Center, CT Healthcare System, U.S. Department of Veterans Affairs, West Haven, CT; 2Department of Internal Medicine, College of Medicine, University of Kentucky, Lexington, KY; 3Space Life Sciences Division, Ames Research Center, National Aeronautics and Space Administration (NASA), Moffett Field, CA; 4Department of Ophthalmology, The Eugene and Marilyn Glick Eye Institute, Indiana University School of Medicine, Indianapolis, IN; 5Department of Integrative and Cellular Physiology, Indiana University School of Medicine, Indianapolis, IN; 6Department of Ophthalmology, University of Florida, Jacksonville, FL

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 (Df). In complex structures such as branching vascular trees, Df is a sensitive measure of space-filling 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 Df by the box-counting method.2 For binary 2D images, Df 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 generated automatically to yield fractal dimension (DF). In complex structures such as branching vascular trees, Df is 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.

RESULTS

By Df, 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 Df, 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.

REFERENCES