Association between Increased Vascular Density and Loss of Protective RAS in Early-Stage NPDR

Krishnan Radhakrishnan1,2, Sneha Raghunandan3, Ruchi J. Vyas4, Amanda C. Vu4, Douglas Bryant5, Duan Yaqian5, Brenda E. Knecht5, Maria B. Grant6,5, KV Chalam2, 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, Kentucky; 3Department of Ophthalmology, The Eugene and Marilyn Glick Eye Institute, Indiana University School of Medicine, Indianapolis, IN; 4Department of Integrative and Cellular Physiology, Indiana University School of Medicine, Indianapolis, IN; 5Department of Ophthalmology, University of Florida, Jacksonville, Florida

PURPOSE

Our hypothesis predicts that retinal blood vessels increase in density during early-stage progression to moderate nonproliferative diabetic retinopathy (NPDR). The prevailing paradigm of NPDR progression is that vessels drop out prior to abnormal, vision-imparing regrowth at late-stage proliferative diabetic retinopathy (DR). However, surprising results for our previous preliminary study1 with NASA’s VESsel GENeration Analysis (VESGEN) software showed that vessels proliferated considerably during moderate NPDR compared to dropout at both mild and severe NPDR. Validation of our hypothesis will support development of successful early-stage regenerative therapies such as vascular repair by circulating angiogenic cells (CACs). The renin-angiotensin system (RAS) is implicated in the pathogenesis of DR and in the function of CACs, a critical bone marrow-derived population that is instrumental in vascular repair.

RESULTS

Arterial and venous patterns were extracted from images of 6 normal control subjects and 3 early NPDR subjects (mild and moderate) obtained by Heidelberg Spectralis® 30 degree imaging following fluorescein angiography (FA). The binary vascular patterns were mapped by VESGEN to yield branching generations (G_i) and quantified that include densities of vessel length (L_i), area (A_i) and number (N_i). Peripheral blood of diabetics and controls was collected for CD34+ CAC isolation. RAS gene expressions in CACs were measured by qPCR for Mas receptor following fluorescein angiography (FA). The binary vascular patterns were mapped by VESGEN to yield branching generations (G_i) and quantified that include densities of vessel length (L_i), area (A_i) and number (N_i). Peripheral blood of diabetics and controls was collected for CD34+ CAC isolation. RAS gene expressions in CACs were measured by qPCR for Mas receptor.

VENUS TREE

CONCLUSIONS

For our ongoing longitudinal study, preliminary evidence by VESGEN indicates that vascular density increased in early NPDR compared to normal retinas. The results are the first independent confirmation of our previous study1. If validated by more complete analysis, the VESGEN discovery is potentially of value for determining optimal therapies at early stages of NPDR, when regenerative vascular treatments are more likely to be successful. These data further support the protective RAS axis within diabetic CACs is lost early in DR and is associated with increased vascular remodeling evidenced by VESGEN analysis.

REFERENCES


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Point of Contact: Patricia Parsons-Wingerter Ph.D., Patricia.A.Parsons-Wingerter@nasa.gov, 650-604-1729

Figure 1 Increased Vascular Density in Early-Stage NPDR

Vessel density increased in both arteries and veins during early NPDR analyzed by NASA’s VESGEN software extracted from 30 degree Spectralis® fluorescein images. Branching generations in the arterial and venous trees (pseudo-colored per legend for Branching Generations, G_i) were automatically analyzed by VESGEN according to physiological vascular rules. All mapped vessels were enlarged slightly to visualize the small vessels. Vessel density was quantified by VESGEN parameters such as densities of vessel length (L_i), area (A_i) and number (N_i). For example, L_i was 2.00 ± 0.06E-2 px/px^2 in NPDR veins for all branching generations compared to 9.85 ± 0.68E-3 px/px^2 in controls, and 1.64 ± 0.13E-2 px/px^2 compared to 9.18 ± 0.99E-3 px/px^2 in arteries. Results, which are slightly updated from our abstract submission, were confirmed by other parameters such as A_i and N_i.

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Point of Contact: Patricia Parsons-Wingerter Ph.D., Patricia.A.Parsons-Wingerter@nasa.gov, 650-604-1729