Revisiting the vascular theory of glaucoma using optical coherence tomography angiography

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Summary
Although glaucoma is the leading cause of irreversible blindness in the world, the exact pathogenesis of it is not fully understood. Mechanical (intraocular pressure, IOP, related mechanical damage) and vascular (ischemic damage due to reduced blood supply) theories are the two commonly proposed theories to explain its pathogenesis. The primary purpose of this thesis was to revisit the vascular theory of glaucoma using optical coherence tomography angiography (OCTA). The thesis also provided an in-depth evaluation of the clinical utility of OCTA in the most common types of glaucoma seen in clinical practice. Most of the work here was conducted in primary open angle glaucoma (POAG), which included both high-pressure OAG and normal-pressure OAG, and in primary angle closure glaucoma (PACG) subjects.

In Chapter 2, the intra-session repeatability of vessel density measurements of OCTA was evaluated in normal eyes and eyes with glaucoma separately and the effect of signal strength index (SSI) of OCTA scans on the repeatability was also evaluated. Three optic nerve head (ONH) scans each of 65 eyes (30 normal, 35 glaucoma eyes) and 3 macular scans each of 69 eyes (35 normal, 34 glaucoma eyes) acquired in the same session with OCTA were analysed. Repeatability estimates of most vessel density measurements were similar in normal and glaucoma eyes. Vessel densities of both peripapillary and macular regions significantly increased with increase in SSI of repeat scans. Knowing the test-retest variability is important to decide the change in vessel density measurements that can be considered clinically significant. This chapter therefore highlights the change in vessel densities over follow-up that can be considered significant and also highlights the importance of incorporating the change in signal strength of the scans while interpreting the change in vessel density measurements.

In Chapter 3, the effect of subject-related (age, gender, systemic hypertension and diabetes), eye-related (refractive error, optic disc size) and technology-related (SSI of the scans) determinants on the peripapillary and macular vessel densities in normal eyes were evaluated. One hundred and eighty-one normal eyes of 107 subjects (45 men, 62 women, median age: 50 years, range: 18-77 years) underwent OCTA imaging. We found that age and optic disc size did not affect the vessel densities of any of the regions. Most of the peripapillary vessel densities
were higher in females. Most of the peripapillary vessel densities were lower, while the parafoveal vessel density was higher, in subjects with hypertension. Most of the vessel densities were lower in subjects with diabetes. SSI showed a statistically significant positive association with the vessel densities of all regions. These results should be considered while interpreting the vessel densities in retinal diseases and glaucoma.

In Chapter 4, the diagnostic ability of the OCTA-measured vessel densities within the ONH, in the peripapillary and macular regions was evaluated. Also, the effect of the covariates, such as disease severity and baseline IOP (pre-treatment IOP) on the diagnostic abilities of vessel densities were evaluated. Seventy-eight eyes of 53 control subjects and 64 eyes of 39 POAG patients underwent OCTA imaging. The area under the receiver operating characteristic curves (AUC) of ONH vessel densities ranged between 0.59 (superonasal sector) and 0.73 (average inside disc), peripapillary between 0.70 (nasal, superonasal and temporal) and 0.89 (inferotemporal), and macular between 0.56 (nasal) and 0.64 (temporal). AUC of the average peripapillary vessel density was significantly better than the average inside disc (p=0.05) and macular (p=0.005) measurement. Diagnostic abilities of vessel densities increased with increasing severity of glaucoma and that of ONH vessel density with higher pre-treatment IOPs.

In Chapter 5, the diagnostic abilities of the OCTA-measured vessel densities within the ONH, in the peripapillary and macular regions in eyes with POAG were compared with that of the OCT-measured neuroretinal rim area, retinal nerve fiber layer (RNFL) thickness and macular ganglion cell complex (GCC) thickness measurements respectively. Seventy-eight eyes of 50 control subjects and 117 eyes of 67 POAG patients underwent vessel density and structural measurements with spectral domain OCT. The AUC of average vessel densities within the ONH, peripapillary and macular region were 0.77, 0.85 and 0.70 respectively. The same of ONH rim area, average RNFL and GCC thickness were 0.94, 0.95 and 0.93 respectively. AUCs of vessel densities were significantly lower (p<0.05) than that of the corresponding structural measurements.

In Chapter 6, the diagnostic abilities of OCTA-measured peripapillary vessel density
were evaluated in eyes with POAG and primary angle closure glaucoma (PACG). Also, the diagnostic abilities of peripapillary vessel densities were compared with RNFL thickness measurements separately in POAG and PACG. Forty-eight eyes of 33 healthy control subjects, 63 eyes of 39 POAG patients and 49 eyes of 32 PACG patients underwent OCTA and RNFL imaging with spectral domain OCT. AUCs of peripapillary vessel density ranged between 0.48 for the temporal sector and 0.88 for inferotemporal sector in POAG. The same in PACG ranged between 0.57 and 0.86. AUCs of all peripapillary vessel density measurements were comparable (p>0.05) to the corresponding RNFL thickness measurements in both POAG and PACG.

In Chapter 7, a more detailed evaluation of the diagnostic abilities OCTA-measured vessel densities within the ONH and in the peripapillary and macular regions in eyes with primary angle closure (PAC, high IOP but normal optic disc and visual field) and PACG was conducted. The diagnostic abilities were compared against those of the rim area, RNFL thickness and GCC thickness measurements. Seventy-seven eyes of 50 control subjects, 65 eyes of 45 patients with PACG, and 31 eyes of 22 PAC patients with a history of high IOP, underwent imaging with OCT. All the vessel density and structural measurements were significantly lower in the PACG compared to the control group. Vessel densities in the PAC were similar to that of the controls; the superotemporal RNFL, however, was significantly thinner in the PAC group (127 μm vs. 135 μm, p=0.01). The AUC and sensitivity at 95% specificity of vessel densities within the ONH (0.76 & 42%) and macular region (0.69 & 18%) in PACG were significantly lower than ONH rim area (0.90 & 77%) and GCC thickness (0.91 & 55%) respectively. AUC and sensitivity of peripapillary vessel density (0.85 & 53%) were statistically similar to RNFL thickness (0.91 & 65%). These results suggest that structural changes in PACG occur earlier than the reduction in retinal vessel densities.

In Chapter 8, the sectoral and global structure-structure association between OCTA-measured peripapillary vessel density and RNFL thickness, and structure-function association between peripapillary vessel density and visual sensitivity loss on perimetry in POAG eyes were evaluated. We also evaluated if fractional polynomial (FP) models characterize the relationships better than linear models.
Structure-structure and structure-function relationships of peripapillary vessel densities were determined in 227 eyes of 143 subjects (63 control and 164 POAG eyes). We found that the $R^2$ values for structure-structure associations using linear models (0.53 for superotemporal sector, 0.61 for inferotemporal and 0.53 for average measurements) were statistically significantly lesser than that determined using FP models (0.57, 0.65 and 0.55 respectively). $R^2$ values for structure-function associations using linear models (0.35 for superotemporal vessel density-inferotemporal visual sensitivity loss, 0.49 for inferotemporal vessel density-superotemporal visual sensitivity loss and 0.39 for average vessel density-average visual sensitivity loss) also were significantly lesser than that determined using FP models (0.43, 0.58 and 0.47 respectively). This demonstrated that FP models were significantly better than linear models in describing these relationships.

In Chapter 9, the measurements of OCTA-derived vessel densities in POAG eyes with disc hemorrhage (DH) were compared with that of severity-matched POAG eyes without DH. Sixty-six eyes of 46 control subjects, 34 eyes of 33 POAG patients with DH (median mean deviation, MD: -3.7 dB) and 63 eyes of 43 POAG patients without DH (median MD: -3.8 dB) underwent imaging with spectral domain OCT. Most of the vessel density and structural measurements were similar ($p>0.05$) in POAG eyes with and without DH. Whole enface vessel density of the disc scan and inferotemporal peripapillary vessel density showed the best AUC and sensitivity at 90% specificity both in POAG eyes with DH (0.82, 56% and 0.75, 59%) and without DH (0.91, 73% and 0.83, 67%). AUCs and sensitivities of vessel density and structural measurements of POAG eyes with and without DH were statistically similar ($p>0.05$). This suggests that the cause of DH in POAG is unlikely to be vascular abnormality.