Supplementary Online Content

Ashraf M, Sampani K, Rageh A, Silva PS, Aiello LP, Sun JK. Interaction between the distribution of diabetic retinopathy lesions and the association of optical coherence tomography angiography scans with diabetic retinopathy severity. *JAMA Ophthalmol.* Published online October 29, 2020. doi:10.1001/jamaophthalmol.2020.4516

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Details of the OCTA segmentation technique

The SVP en face OCTA image was segmented with an inner boundary of 3 µm below the internal limiting membrane and an outer boundary set at the inner plexiform layer (IPL)-inner nuclear layer (INL) junction. The ICP en face OCTA image was segmented with an inner boundary set at the IPL-INL junction and an outer boundary set at 20 µm below the IPL-INL junction. The DCP en face OCTA image was segmented with an inner boundary set at 20 µm below the IPL-INL junction and an outer boundary set at 15 µm below the outer plexiform layer (OPL)-outer nuclear layer (ONL) junction.

OCTA manual processing technique

The en face OCTA images for the SVP, ICP and DCP were exported to ImageJ for post imaging processing (National Institutes of Health, Bethesda, MD, USA). The parafoveal area was cropped from the image (inner ring 1.5 mm diameter and outer ring 3 mm) and using a technique previously described the image was binarized (eFigure 1).[1-4] In brief, after using a 'top hat filter', images were duplicated, with one image being processed using a hessian filter followed by global Huang thresholding and the second image being binarized using local median thresholding. Only pixels common to both images were used to generate a final image that was analyzed quantitatively. For each OCTA image, vessel density (VD) was calculated as the percentage of area occupied by perfused vessels. In addition, for SVP images 'Max Entropy' thresholding function was used on ImageJ to delineate the large and medium sized superficial vessels.[5] These in turn were subtracted from the SVP to generate the superficial capillary plexus (SCP) (eFigure 1).

eReferences

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2. Borrelli E, Lonngi M, Balasubramanian S, et al. Macular Microvascular Networks in Healthy Pediatric Subjects. Retina. Jun 2019;39(6):1216-1224.
3. Uji A, Balasubramanian S, Lei J, Baghdasaryan E, Al-Sheikh M, Sadda SR. Impact of Multiple En Face Image Averaging on Quantitative Assessment from Optical Coherence Tomography Angiography Images. Ophthalmology. Jul 2017;124(7):944-952.
4. Ashraf M, Sampani K, Abu-Qamar O, et al. Optical Coherence Tomography Angiography Projection Artifact Removal: Impact on Capillary Density and Interaction with Diabetic Retinopathy Severity. Translational vision science & technology. Jun 2020;9(7):10.
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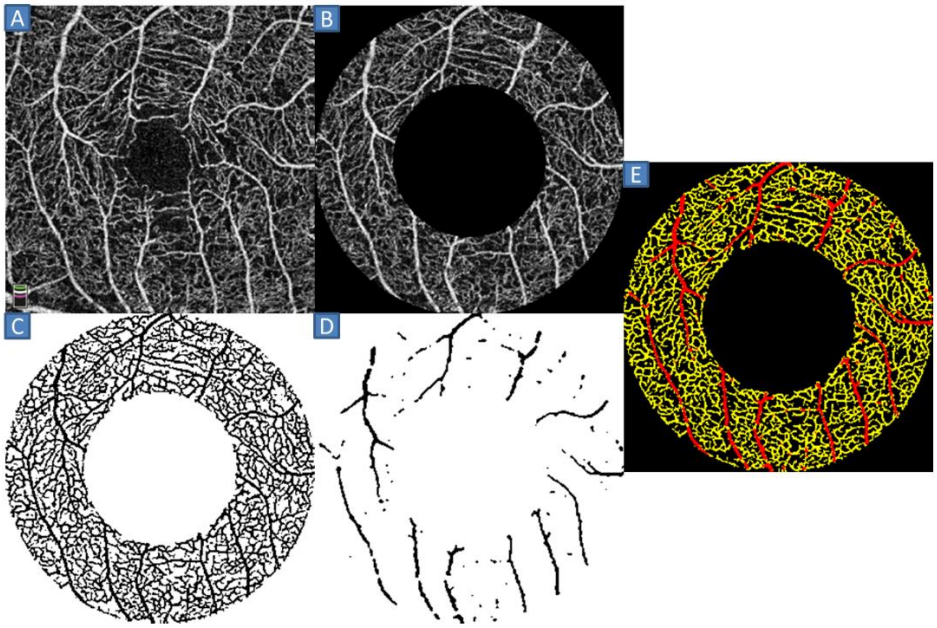
eFigure. Binarization Technique for the Superficial Vascular Complex (SVC)

(A) SVC images (B) Parafoveal zone cropped from original image (C) Parafoveal image binarized (D) Large and medium vessels extracted from binarized imaged (E) Overlay showing large/medium vessels (red) and small capillary vessels (yellow).



eTable 1. Comparison of Optical Coherence Tomography Angiography (OCTA) Parameters Between Eyes With and Without Predominantly Peripheral Lesions (PPL) Stratified by Diabetic Retinopathy (DR) Severity

	No PPL (Mean ± SD)	PPL (Mean ± SD)	Unadjusted p-value	GEE* (p-value)
Mild NPDR				
Parafovea VD SCP (%)	38.08±4.69	34.05±4.06	.03	.19
Parafovea VD ICP (%)	45.20±3.01	45.00±1.68	.41	.99
Parafovea VD DCP (%)	45.81±2.95	44.53±1.68	.23	.84
Choriocapillaris (%)	69.68±6.18	67.07±5.62	.15	.59
Moderate NPDR				
Parafovea VD SCP (%)	36.43±4.63	35.20±4.05	.26	.31
Parafovea VD ICP (%)	45.33±1.56	45.47±1.36	.64	.31
Parafovea VD DCP (%)	45.82±2.22	45.38±1.44	.38	.81
Choriocapillaris flow density (%)	67.57±5.55	69.29±4.61	.23	.45
Severe NPDR – PDR				
Parafovea VD SCP (%)	34.05±4.06	36.03±4.30	.05	.18
Parafovea VD ICP (%)	45.00±1.68	45.21±2.01	.58	.73
Parafovea VD DCP (%)	44.53±1.68	44.94±1.45	.21	.85
Choriocapillaris flow density (%)	67.07±5.62	68.29±5.63	.44	.57

* General estimating equations (GEE) correcting for age, SSI, SE, type of DM, DM duration and correlation of both eyes

PPL; predominantly peripheral lesions, SD; standard deviation, NPDR; non-proliferative diabetic retinopathy, VD; vessel density, SCP; superficial capillary plexus, ICP; intermediate capillary plexus, DCP; deep capillary plexus

eTable 2. Parafoveal Vessel Density in Eyes With Predominantly Peripheral Lesions (PPL) After Cropping Central Circles of 1 mm and 0.5 mm

	Mild NPDR (Mean ± SD)	**Moderate NPDR (Mean ± SD)**	**Severe NPDR/PDR (Mean ± SD)**	**GEE* (p-value)**
Parafoveal Vessel Density After cropping a central 1.0 mm circle				
Parafovea VD SCP (%)	37.03±3.38	35.36±3.42	35.95±3.74	.157
Parafovea VD DCP (%)	45.37±1.25	44.76±1.49	44.70±1.60	.107
Parafoveal Vessel Density After cropping a central 0.5 mm circle				
Parafovea VD SCP (%)	37.96±3.08	36.39±3.39	37.48±3.56	.175
Parafovea VD DCP (%)	46.42±1.17	45.88±1.52	45.95±1.63	.251

* General estimating equations (GEE) correcting for age, SSI, SE, type of DM, duration of DM and correlation of both eyes

PPL; predominantly peripheral lesions, SD; standard deviation, NPDR; non-proliferative diabetic retinopathy, VD; vessel density, SCP; superficial capillary plexus, ICP; intermediate capillary plexus, DCP; deep capillary plexus,

eTable 3. Sensitivity Analysis Evaluating a Subset of Eyes in the No Predominantly Peripheral Lesions (PPL) Group That Was Matched to the PPL Group With Regards to Diabetic Retinopathy Severity and Type of Diabetes Mellitus

	Mild NPDR (84) (Mean ± SD)	**Moderate NPDR (36) (Mean ± SD)**	**Severe NPDR/PDR (41) (Mean ± SD)**	**GEE* (p-value)**
Parafovea VD SCP (%)	38.10 ± 4.69	36.43 ± 4.63	33.99 ± 3.67	<.01
Parafovea VD ICP (%)	45.04 ± 1.55	45.33 ± 1.56	44.84 ± 1.76	1.00
Parafovea VD DCP (%)	45.76 ± 3.18	45.82 ± 2.22	44.77 ± 1.56	.14
Choriocapillaris flow density (%)	69.89 ± 6.64	67.57 ± 5.55	68.21 ± 6.18	.06

* General estimating equations (GEE) correcting for age, SSI, SE, type of DM, duration of DM and correlation of both eyes

PPL; predominantly peripheral lesions, SD; standard deviation, NPDR; non-proliferative diabetic retinopathy, VD; vessel density, SCP; superficial capillary plexus, ICP; intermediate capillary plexus, DCP; deep capillary plexus,