Kidney International

The eye, the kidney & cardiovascular disease:

old concepts, better tools & new horizons

Supplementary appendix

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Short title: Retinal imaging & the kidney

Contents

1. Supplementary table 1. *Retinal vascular metrics to predict incident hypertension*

Study	Country	n	Population Mean age	Retinal metric	Clinical outcome	Mean BP	Diabetes	Follow up	Results
Wong[S1] 2004 Prospective, Population - based cohort	US	5,628	Normotensive, white and African-American adults 59 years	AVR	Incident hypertension: BP ≥140/90mmHg or use of anti-hypertensives	115/68 mmHg	8%	3 years	14% developed hypertension Smallest AVR quintile predicts incident hypertension Adjusted OR 1.6 (1.2-2.2) *vs.* widest quintile
Wong[S2] 2004 Prospective, Population - based cohort	US	2,451	Normotensive, white adults 60 years	AVR CRAE CRVE	Incident hypertension: BP ≥140/90mmHg or use of anti-hypertensives	125/75 mmHg	6%	10 years	29% developed hypertension Smallest AVR quartile predicted incident hypertension:adjusted OR 1.8 (1.4-2.4) *vs.* widest Similar association for CRAE No association for CRVE
Smith[S3] 2004 Prospective, Population - based cohort	Australia	1,319	Adults with BP ≤159/99 mmHg 64 years	AVR CRAE CRVE	Incident severe hypertension: BP ≥160/100 mmHg or use of anti-hypertensives	136/80 mmHg	6%	5 years	30% developed severe hypertension Smallest AVR and narrowest CRAE quintile predicted incident hypertension *vs.* widest AVR: adjusted OR 2.0 (1.3-3) CRAE: adjusted OR 2.1 (1.4-3.3) No association for CRVE
Ikram[S4] 2006 Prospective, Population - based cohort	Netherlands	1,900	Normotensive adults 64 years	AVR CRAE CRVE	Incident hypertension: BP≥140/90mmHg or use of anti-hypertensives	122/69 mmHg	4%	7 years	42% developed hypertension Smallest quartile of AVR, narrowest CRAE and CRVE associated with incident hypertension AVR: Adjusted OR 1.7 (1.3-2.4) CRAE: Adjusted OR 2.2 (1.6-2.9) CRVE: Adjusted OR 1.4 (1.01-3)
Kawasaki[S5] 2009 Prospective,	US	2,583	Multi-ethnic normotensive adults 60 years	CRAE CRVE	Incident hypertension: BP ≥140/90mmHg or use of anti-hypertensives	114/69 mmHg	6%	3 years	17% developed hypertension Narrower CRAE predicted incident hypertension: adjusted OR 1.5 (1.01-2.14) Persisted only in white subjects

Population - based cohort									Wider CRVE associated with incident hypertension: adjusted OR 1.7 (1.13-2.53)
Tanabe[S6] 2010 Prospective, Population - based cohort	Japan	310	Normotensive adults 57 years	CRAE CRVE (n=310)	Incident hypertension: BP≥140/90mmHg or use of anti-hypertensives	117/71 mmHg	Undefined	5 years	32% developed hypertension Narrowest CRAE tertile predicted incident hypertension: adjusted OR 2.4 (1.1-5) Lost significance when further adjusted for BP: adjusted OR 2.1 (0.9-4.7) *vs.* widest No association for CRVE

BP – blood pressure, AVR – arteriole-to-venule ratio, OR – odds ratio, CRAE – central retinal arteriolar equivalents, CRVE – central retinal venular equivalents. All values are mean.

2. Supplementary table 2. *Retinal vascular metrics to predict incident diabetes mellitus*

Study	Country	n	Population Mean age	Retinal metric	Clinical outcome	Hypertension	Mean BP	Follow up	Results
Wong[S7] 2002 Prospective, Population - based cohort	US	7,993	Non-diabetic White and African-American adults 59 years	AVR	Incident diabetes: Fasting glucose ≥7 mmol/L, random glucose ≥11.1 mmol/L or use of anti-diabetic medicines	34%	122/72 mmHg	3.5 years	4% developed diabetes Smallest AVR quartile predicted incident diabetes: adjusted OR 1.7 (1.1-2.6) *vs.* largest quartile
Wong[S8] 2005 Prospective, Population - based cohort	US	3,251	Non-diabetic adults 60 years	AVR CRAE CRVE	Incident diabetes: random glucose ≥11.1 mmol/L	33%	127/78 mmHg	10 years	8% developed diabetes Smallest quintile AVR predicted incident diabetes: adjusted RR 1.5 (1.03-2.6) *vs.* largest quartile Narrowest CRAE quintile associated with incident diabetes but not when adjusting for other risk factors such as BP RR greatest in those with smallest AVR and known hypertension: adjusted RR 3.4 (1.7-4) *vs.* largest AVR and normotensive No association with CRVE
Ikram[S9] 2006 Prospective, Population - based cohort	Netherlands	2,309	Non-diabetic adults 65 years	AVR CRAE CRVE	Incident diabetes: Fasting glucose ≥7mmol/L Incident impaired fasting glucose (IFG): Fasting glucose 6.1-7.0mmol/L	No data	134/74 mmHg	6.4 years	13% developed IFG 5% developed diabetes Smaller AVR and wider CRVE associated with IFG Adjusted ORs for IFG AVR: 1.15 (0.99-1.3) (per SD decrease) CRVE: 1.14 (0.98-1.3) (per SD increase) Adjusted ORs for diabetes: AVR: 1.08 (0.86-1.4) (per SD decrease) CRVE: 1.09 (0.87-1.4) (SD increase) No association with CRAE
Nguyen[S10] 2008	Australia	803	Non-diabetic adults; adults with impaired glucose tolerance	CRAE CRVE	Incident diabetes: Fasting glucose ≥7.0 mmol/l, 2-hour plasma	45%	135/72 mmHg	5 years	13% developed diabetes

Prospective, Population - based cohort			and impaired fasting glucose 57 years		glucose ≥11.1 mmol/l or use of diabetic medications				Narrowest CRAE tertile predicted development of diabetes: adjusted OR 2.2(1.02-4.8*) vs.* widest tertile No assocation for CRVE
Kifley[S11] 2008 Prospective, Population - based cohort	Australia	2,123	Non-diabetic adults 64 years	CRAE CRVE	Incident diabetes and IFG: Incident diabetes: Fasting glucose ≥7mmol/L Incident impaired (IFG): Fasting glucose 6.1-7.0mmol/L	68%	144/83 mmHg	10 years	9% developed diabetes 6% developed IFG 13% developed diabetes or IFG Wider CRVE predicted incident IFG only: adjusted OR 1.5 (1.1-2.1) for each SD increase in venular calibre No associations for CRAE

BP – blood pressure, AVR – arteriole-to-venule ratio, OR – odds ratio, CRAE – central retinal arteriolar equivalents, CRVE – central retinal venular equivalents, RR – risk ratio, IFG – impaired fasting glucose. All values are mean.

3. Supplementary table 3. *Retinal vascular metrics to predict cardiovascular disease outcomes*

Study	Country	n	Population Mean age	Retinal metric	Clinical outcome	Hypertension	Mean BP	Diabetes	CKD	Pre-existing CVD	Follow up	Results
Coronary heart disease												
Wong[S12] 2002 Prospective, Population - based cohort	US	9648	White and African-American adults 60 years	AVR	Incident CHD: fatal/non-fatal myocardial infarction, revascularisation	40%	89 mmHg (mean arterial pressure)	17%	No data	No data	3.5 years	3% developed CHD Smallest 2 AVR quintiles associated with an increased risk of incident CHD in **women only**: lowest AVR quintiles adjusted RRs: Q1 2.2 (1-4.6) and Q2 2.3(1-4.8) *vs.* largest. Relationship strongest in women without hypertension or diabetes and for myocardial events rather than revascularisation.
Wang[S13] 2006 Prospective, Population - based cohort	Australia	3340	White adults 65 years	AVR CRAE CRVE	CHD mortality: defined by national health database ICD coding	45%	146/84 mmHg	7%	No data	13%	9 years	6% died from CHD For women < 75 years old, smallest AVR quartiles associated with nearly 3-fold increased risk of CHD mortality *vs.* largest quartile Narrower CRAE and wider CRVE associated with greater risk of CHD mortality per SD change: Women <75 years CRAE adjusted HR 1.5 (1.1-2.2) CRVE adjusted HR 1.5 (1.1-2.2) Men <75 years CRAE adjusted HR 1.1 (0.8-1.4) CRVE adjusted HR 1.4 (1.1-1.8) No associations in >75 years olds regardless of gender.
Liew[S14] 2011 Prospective, Population - based cohort	Australia	3303	White adults 65 years	*Df*	CHD mortality: defined by national health database ICD coding	70%	146/84 mmHg	7%	No data	16%	14 years	14% died from CHD Highest and lowest quartiles of *Df* associated with increased risk of CHD mortality:

												Lowest *Df* adjusted HR 1.5 (1.2-1.9) Highest *Df* adjusted HR 1.6 (1.2-2.1) In those <70 years suboptimal *Df* associated with nearly 2-fold greater risk of CHD mortality
Stroke												
Wong[S15] 2001 Prospective, Population - based cohort	US	10358	White and African-American adults 54 years	AVR	Incident stroke: defined by subject recall, health records and ICD coding of hospital admissions and discharges	33%	120/77 mmHg	10%	No data	4% (coronary disease)	3.5 years	1% had an ischaemic stroke Smallest AVR quintile associated with greatest risk of any incident stroke and ischaemic stroke: unadjusted RR 2.35 and 2.3; age, gender and race adjusted RR 1.98 and 1.91, *vs.* widest respectively. No association when adjusted for BP, diabetes, hypertension, smoking and lipids
Mitchell[S16] 2005 Prospective, Population - based cohort	Australia	3583	White adults 68 years	AVR	Incident stroke and stroke death defined by subject recall, health records and ICD hospital admission and discharge codes	49%	147/84 mmHg	6%	No data	No data	5 years	3% of patients had a stroke or died from a stroke AVR not associated with incident stroke events in adjusted analyses.
Ikram[S17] 2006 Prospective, Population - based cohort	Netherlands	5540	White adults with no prior stroke 67 years	AVR CRAE CRVE	Incident stroke: from health records and neuroimaging; Subdivided into infarction or haemorrhage	No data	138/73 mmHg	9%	No data	No data	8.5 years	7% had a stroke, nearly 2/3 of these were infarcts. Wider CRVE and smaller AVR as quartiles and continuous variables were associated with increased risk of stroke, particularly infarction CRVE age, sex adjusted HR: 1.3 (1.03-1.6) AVR age, sex adjusted HR: 1.5 (1.2-1.9) CRVE association remained when adjusted for CVD risk factors No associations with CRAE

Yatsuya[S18] 2010 Prospective, Population - based cohort	US	10496	White and African-American adults 59 years	CRAE CRVE	Incident ischaemic stroke: defined from health records, ICD admission and neuroimaging; Strokes subclassified into lacunar, non-lacunar, cardioembolic	29%	121 mmHg (systolic BP)	14%	No data	No data	11 years	3% suffered an ischaemic stroke, of which 20%were lacunar. Narrower CRAE associated with increased risk lacunar stroke both as narrowest quintile *vs*. widest (adjusted HR 5.2(1.9-14.1)) and as continuous variable per SD decrease (HR 1.7(1.2-2.3)) Wider CRVE associated with increased risk of lacunar stroke as continuous variable, adjusted HR 1.4 (1.1-1.9) No association with non-lacunar or cardioembolic events
Wieberdink[S19] 2010 Prospective, Population - based cohort	Netherlands	5518	White adults with no prior stroke 67 years	CRAE CRVE	Incident stroke: from health records and neuroimaging; Subdivided into infarction or haemorrhage	55%	138/73 mmHg	10%	No data	3%	11.5	11% had a first stroke, 58% infarction, 10% haemorrhage, remainder undefined Wider CRVE as a continuous variable or quartiles was associated with increased risk of any stroke, infarcts and haemorrhagic strokes: Stroke adjusted HR 1.2 (1.1-1.3) Infarction adjusted HR 1.3 (1.1-1.5) Haemorrhage adjusted HR 1.5 (1-2) (all per SD increase) Narrower CRAE had borderline associations with stroke risk, except for anticoagulation-associated intracerebral haemorrhage
Cheung[S20] 2013 Prospective, Population - based cohort	Singapore	2644	Malay adults without prior stroke 57 years	CRAE CRVE Tortuosity *Df* Branching angles	Incident stroke: from health records	66%	145/80 mmHg	22%	91umol/L	No data	4.4 years	2% had a stroke, 85% ischaemic Wider CRVE was associated with increased risk of stroke, both as widest quartile *vs*. narrowest (adjusted HR 3.3, 1.3-8.6) and as continuous increasing variable (1.3, 1-1.6) No other vascular metrics associated with risk of stroke.

												Addition of retinal metrics to clinical tools improved stroke risk stratification by ~9%
Coronary heart disease and stroke												
Wong[S21] 2003 Population-based, nested case-control	US	413 CVD deaths 1198 controls	White adults Age not reported	AVR	Cardiovascular mortality: ICD coding of fatal myocardial infarction or stroke	70% in those with CVD death 60% in controls	140/74 mmHg 136/75 mmHg	24% 9%	No data	43% 22%	10 years	Lowest AVR quintile associated with increased risk of CVD mortality: Adjusted RR 1.5 (1.1-2.1) mainly in younger subjects (43-74 years)
Wong[S22] 2006 Prospective, Population - based cohort	US	1992	Predominantly white adults >65 years with no prior CVD 78 years	CRAE CRVE	Incident CVD: Incident CHD: fatal/ non-fatal myocardial infarction, other CHD death; Incident stroke: fatal/ non-fatal stroke	58%	130/67 mmHg	15%	No data	0%	5 years	CHD events 6% Stroke events 6% Narrowest CRAE and widest CRVE quartile associated with increased risk of CHD events *vs.* widest/narrowest respectively: CRAE adjusted HR: 2 (1.1-3.8) CRVE adjusted HR: 3 (1.6-5.8) Stronger associations for CRVE in those>80, diabetics and hypertensive Widest CRVE quartile only associated with increased risk of stroke: adjusted HR 2.2 (1-4.3)
Wang 2006[S23] Prospective, Population - based cohorts	US and Australia	7494	Predominantly white adults >90% 63 years	CRAE CRVE	Incident CVD mortality: death from stroke or CHD	58%	No data	8%	No data	22%	11 years	CHD deaths 9% Stroke deaths 4% Narrowest CRAE and widest CRVE quintile associated with increased risk of death from coronary heart disease *vs.* other quintiles: CRAE adjusted HR: 1.3 (1.1-1.6) CRVE adjusted HR: 1.2 (1.0-1.5) Associations strongest in the US cohort and those <70 years No associations between CRVE or any continuous retinal vascular metric and incident stroke mortality in adjusted analyses

Siedelmann[S24] 2016 Prospective, Population - based cohort	US	10470	White and African-American adults without prior CVD or heart failure 59 years	CRAE CRVE AVR	Incident CVD events and death: myocardial infarction, revascularisation, stroke, heart failure	30%	125 mmHg (systolic BP)	14%	No data	0%	16 years	1778 coronary events 548 stroke events 1395 heart failure events 26% mortality Narrower CRAE associated with increased risk of death (adjusted HR 1.14) and stroke (adjusted HR 1.06) in all subjects; Wider CRVE showed stronger associations for both stroke and death. Narrower CRAE/wider CRVE associated with increased CHD in women only Addition of retinal metrics to clinical tools improved CVD event risk stratification by 11%
Yip[S25] 2017 Prospective, Population - based cohort	Singapore	3496	Malay adults without prior CVD 58 years	CRAE CRVE	Incident CVD events defined as: myocardial infarction, stroke and cardiovascular death certificate coding	58%	140/82	38%	77mls/min	0	5.8 years	4% developed overt CVD Wider CRVE as a continuous variable or quartiles was associated with increased risk of CVD events: Adjusted HR 2.1(1.2-3.7) *vs* narrowest quartile. No relationship between CRAE and CVD events. Association of venular widening with microalbuminuria was associated with greater risk of incident CVD than either measure alone

BP – blood pressure, AVR – arteriole-to-venule ratio, OR – odds ratio, CRAE – central retinal arteriolar equivalents, CRVE – central retinal venular equivalents, RR – risk ratio, IFG – impaired fasting glucose, HR – hazard ratio, eGFR – estimated glomerular filtration rate, CKD – chronic kidney disease. *Df* - fractal dimension, CVD – cardiovascular disease, CHD – coronary heart disease, ICD – International Classification of Diseases. All values are mean.

4. Supplementary figure legends

Supplementary figure 1. *Alport syndrome-associated retinopathy*.

Ultra-wide field scanning laser ophthalmoscope photograph of left eye from a male patient with end-stage renal disease secondary to X-linked Alport syndrome. The characteristic dot-and-fleck retinopathy is evident as green peri-macular deposits in the centre of the image. There is also associated loss of foveal reflex due to macular thinning. The presence of Alport-associated retinopathy can help diagnosis, suggest inheritance patterns, identify those at risk of progressive CKD and differentiate from mimics such as thin GBM disease which has no associated retinal features.[S26, 27]

Supplementary figure 2. *Retinal photography and fundus retinal calibre assessment*

A. Right eye digital retinal photograph using Canon CR-1 fundus camera with a field of view of 45°.

B. Right eye scanning laser ophthalmoscope image centred over optic disc using the Heidelberg SPECTRALIS® Spectral-Domain OCT machine (SD-OCT, Heidelberg Engineering, Heidelberg, Germany). The centre of the optic disc is manually determined. A standard set of concentric circular measurement zones commonly used in the analysis of fundus camera images is mapped from this point as shown. Zone 'A' is the area 0.5 to 1 optic disc diameters away from the centre as bounded by the white dotted lines. The vessel analysis software VAMPIRE® (University of Dundee, United Kingdom) selects the six widest arterioles (red) and venules (blue) crossing zone A to calculate CRAE, CRVE and AVR.

Supplementary figure 3. *Retinal optical coherence tomography*.

Blue lines represent fibre paths. *Red lines* represent optical paths. *Green lines* represent signal paths. Low coherence light (typically ~800 nm wavelength) is split into a sample beam and

reference beam. The sample beam is shone onto the retina and reflected back as 'light echoes'. The reference beam is directed to a mirror positioned at a known distance from the light source. A range of 'sample' light echoes each return at different times depending on the distance of the reflecting tissue from the light source. Returning 'sample' and 'reference' light echoes are re-united and directed to a photodetector. An interference signal is detected when the time delays between the 'sample' and 'reference' light echoes is small*, i.e*. the distance of reference mirror matches the distance of the reflecting tissue. Moving the reference mirror (positions A to C) alters the distance the reference beam/echo must travel and thus changes the time delay between reference and sample echoes. At each new reference mirror distance, the reference echo time delay will closely match a different sample echo time delay, generating a new interference signal corresponding to a deeper/shallower reflecting tissue layer. Sequential movement of reference mirror allows the construction of a single interference depth profile: the A-scan. A-scans obtain depth profiles along the z-axis. The lateral scanning mirror is rotated through positions 1 to 4 along the x–axis to obtain sequential adjacent A-scans which are used to generate a single horizontal B-scan. The vertical scanning mirror is elevated/lowered along the y-axis to obtain horizontal B-scans at multiple levels. B-scans can then be stacked to create a volume scan (**Supplementary videos 1 and 2**).

Supplementary figure 4. *Retinal layer segmentation by OCT.* Close up of horizontal line OCT scan through the macula of the right eye using the Heidelberg SPECTRALIS® SD-OCT (Heidelberg Engineering, Heidelberg, Germany) with automated segmentation of individual retinal layers. RNFL – retinal nerve fibre layer, GCL – ganglion cell layer, IPL – inner plexiform layer, INL – inner nuclear layer, OPL – outer plexiform layer, ONL – outer nuclear layer, PR – photoreceptor layer, RPE – retinal pigment epithelium, BM – Bruch's membrane, CH – choroid.

Supplementary figure 5. *OCT angiography*

Right eye 3 x 3mm OCT angiograms *en face* (left panels) and in cross-section (right panels), centred on the macula, using the AngioVue® Imaging System (Optovue, Inc., Freemont, California).

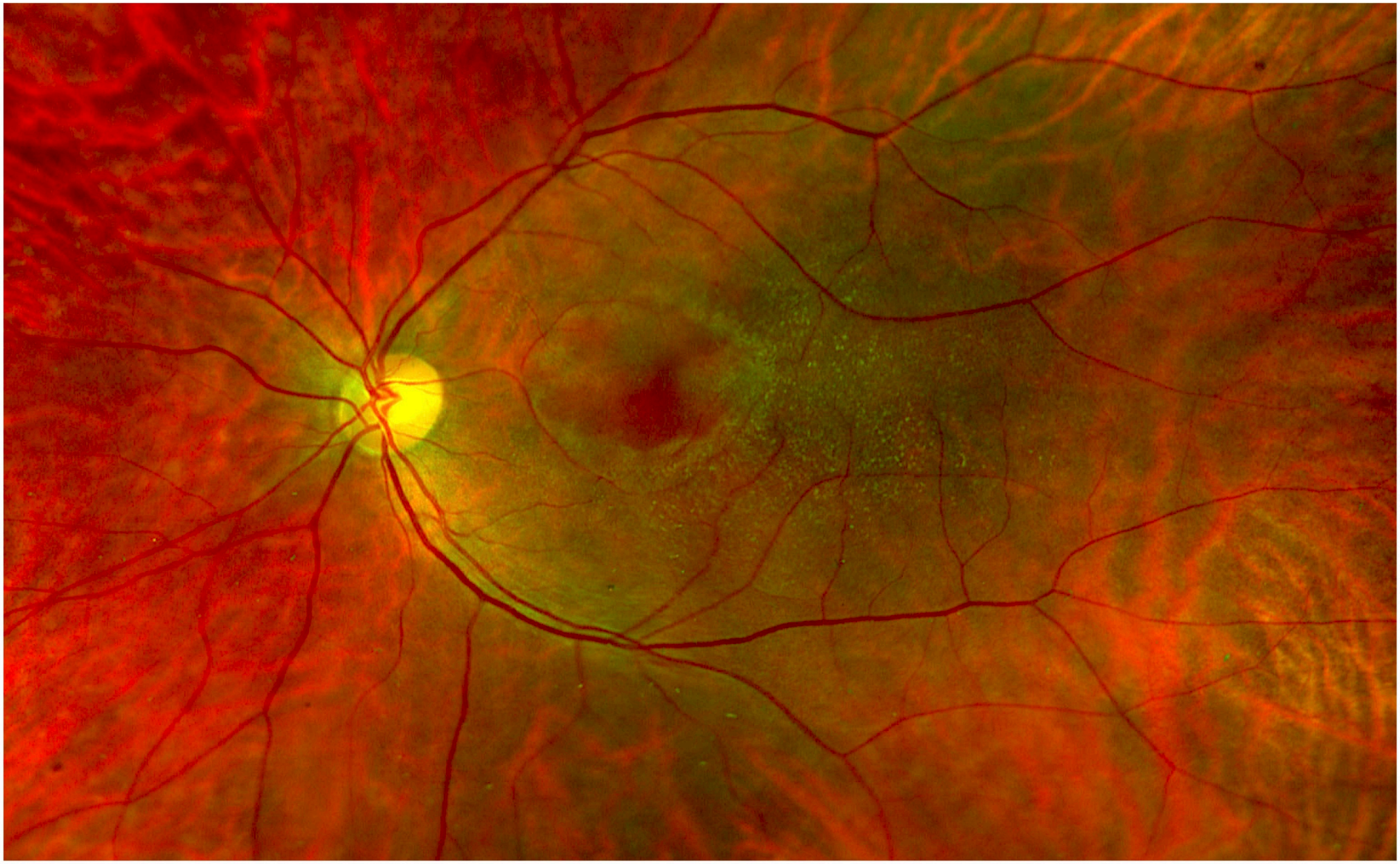
A. *Left panel:* The peri-macular superficial capillary plexus and the foveal avascular zone. *Right panel:* OCT image showing the level and boundaries of retinal layer segmentation the corresponds to *en face* angiogram. Red and green lines define the upper and lower limits respectively, of the segmentation band.

B. *Left panel:* The peri-macular deep capillary plexus and the foveal avascular zone. *Right panel:* OCT image showing the level and boundaries of deeper retinal layer segmentation the corresponds to *en face* angiogram. Red and green lines define the upper and lower limits respectively, of the segmentation band.

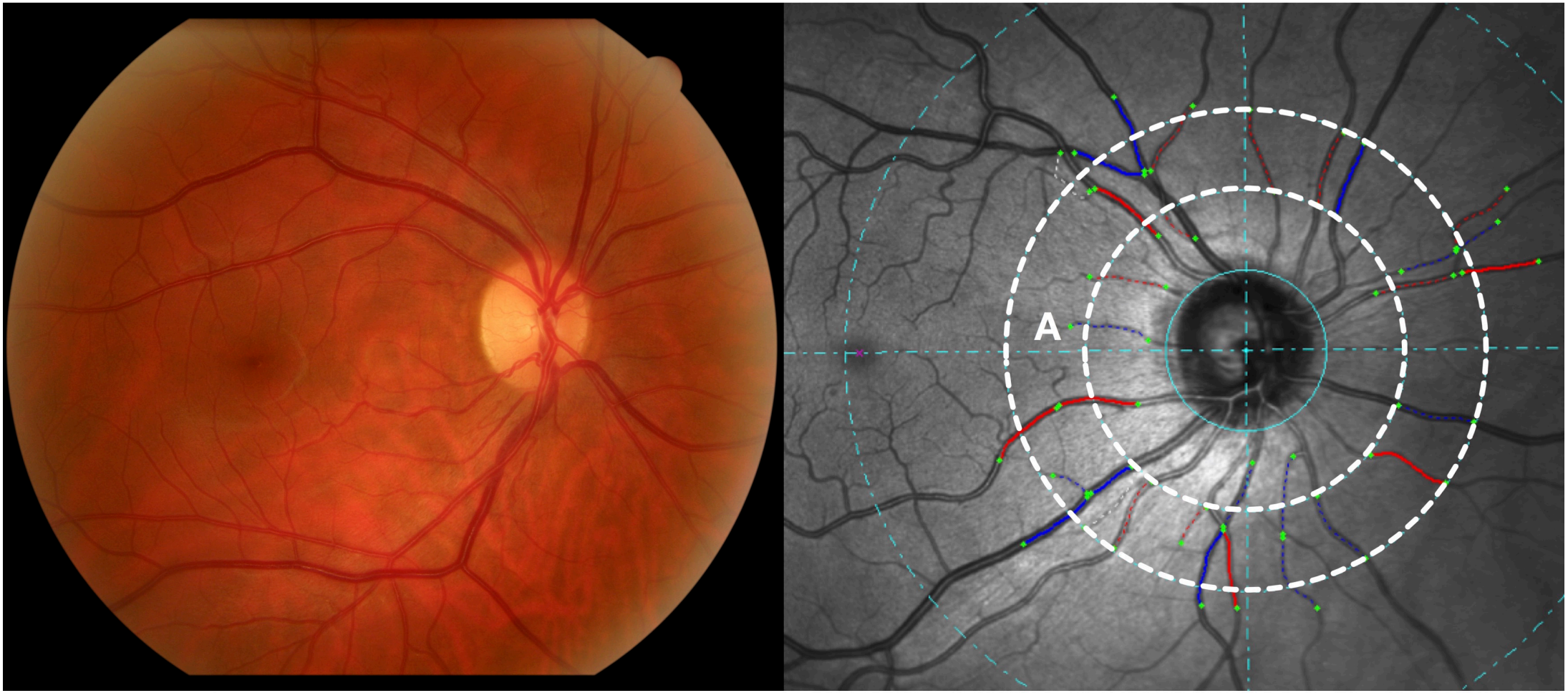
C. *Left panel:* The outer (deepest) retinal layers are relatively avascular as shown and is thus dependent on passive oxygenation from the deeper choroidal circulation. *Right panel:* OCT image showing the level and boundaries of outer retinal layer segmentation the corresponds to *en face* angiogram. Red lines define the upper and lower limits of the segmentation band.

D. *Left panel:* The subfoveal choriocapillaris is a dense mesh of capillaries underneath the pigment epithelium. Despite advances in OCT-A, imaging discrete vessels here remains challenging. *Right panel:* OCT image showing the level and boundaries of choriocapillaris segmentation the corresponds to *en face* angiogram. Red and green lines define the upper and lower limits respectively, of the segmentation band.

Supplementary figure 1 Alport syndrome-associated retinopathy

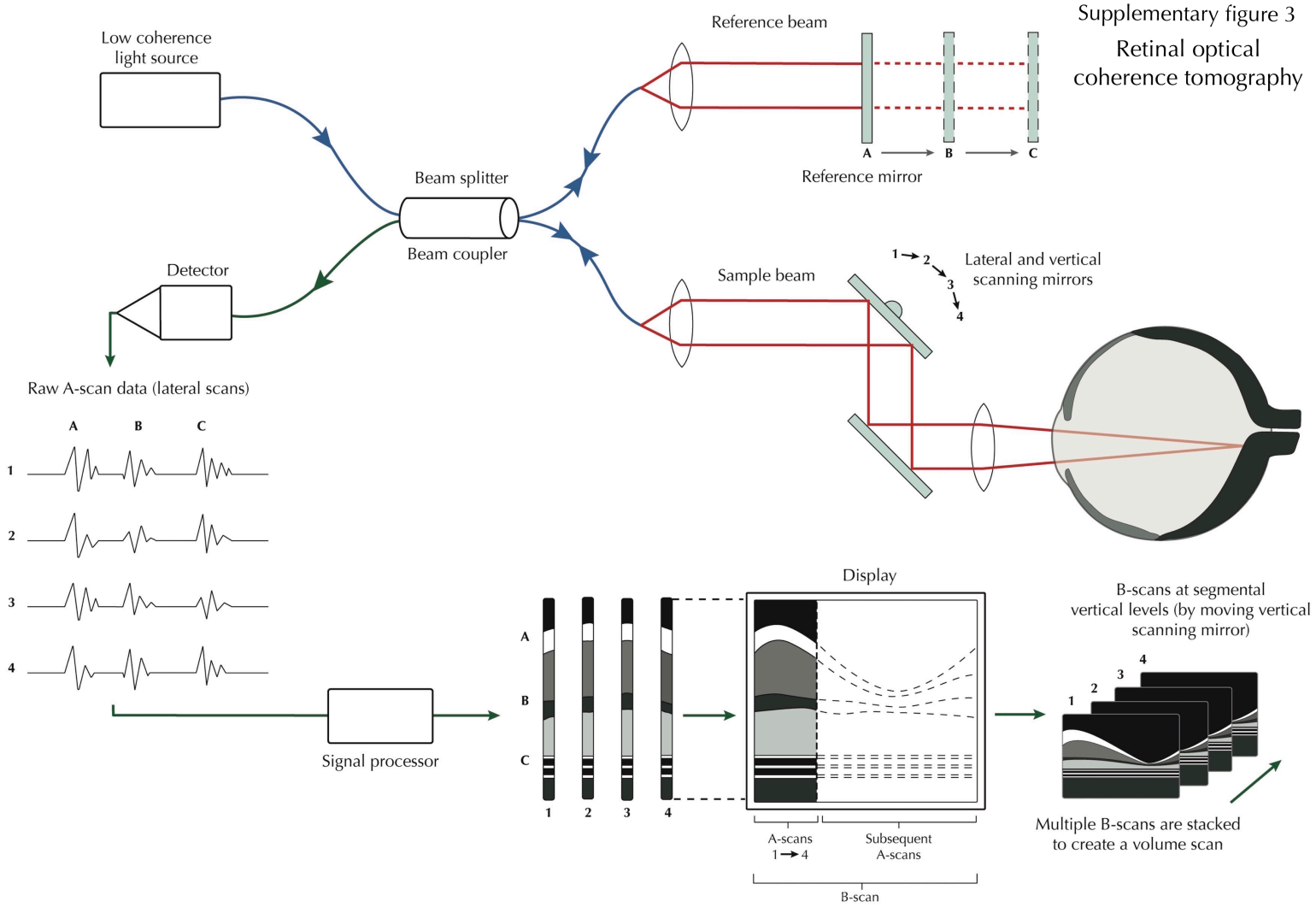


Supplementary figure 2 Retinal photography and fundus retinal calibre assessment

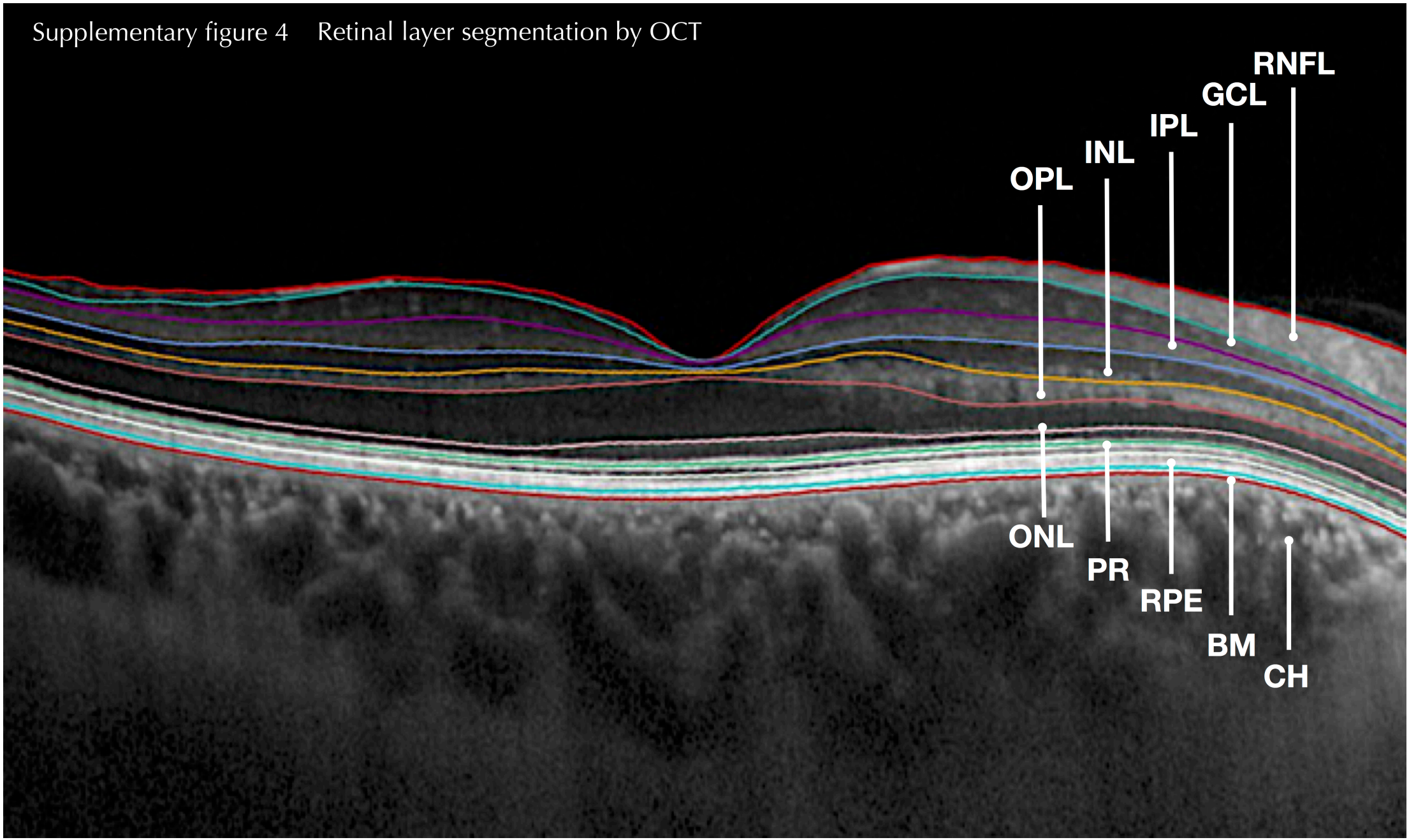


Supplementary figure 3

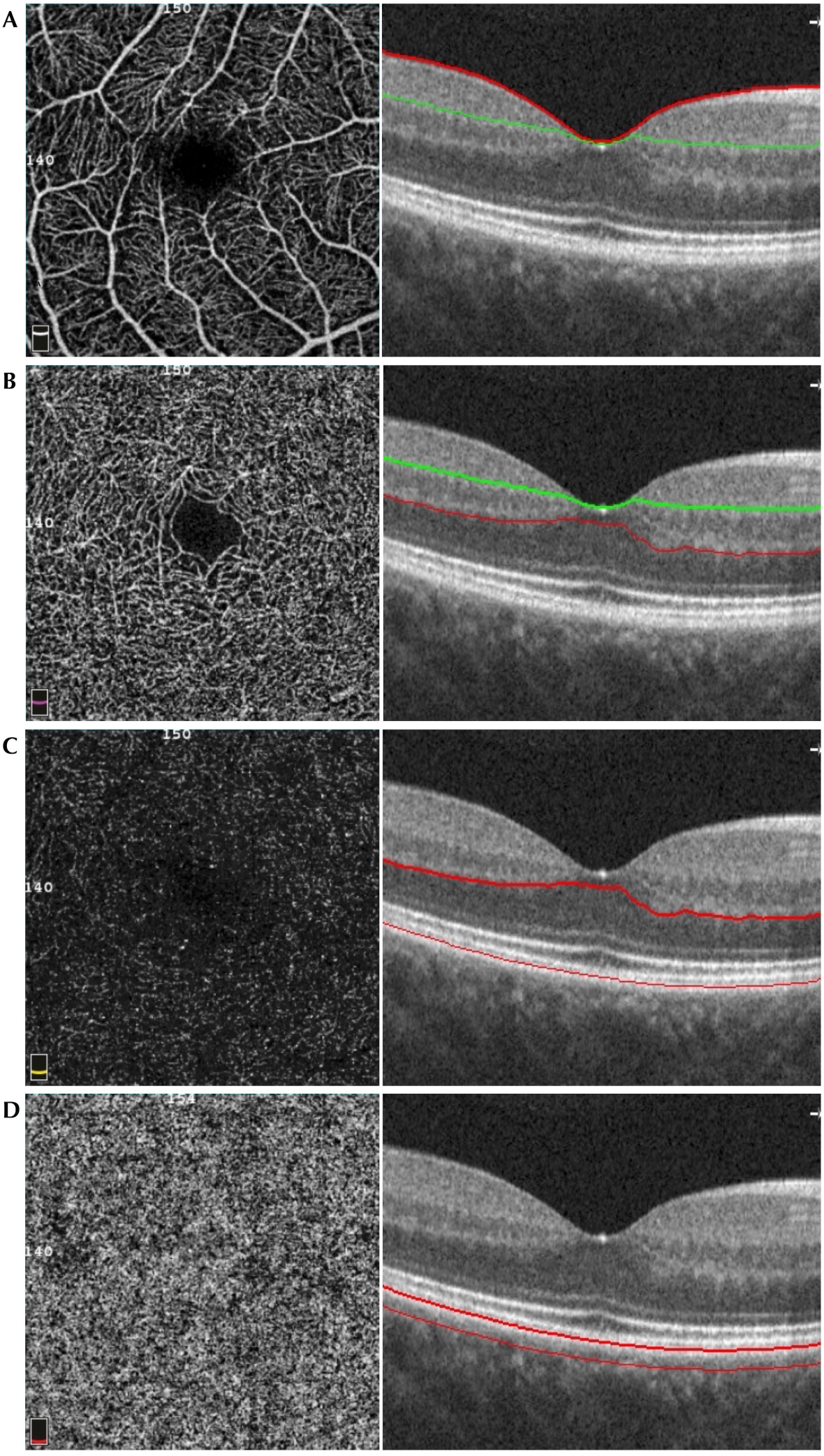
Retinal optical coherence tomography



Supplementary figure 4 Retinal layer segmentation by OCT



Supplementary figure 5 OCT angiography



10. Supplementary video legends

Supplementary video 1. *OCT in health*

Video of a 3-dimensional rendered macular volume OCT scan of right eye from a healthy volunteer.

Supplementary video 2. *OCT in CKD*

Video of a 3-dimensional rendered macular volume OCT scan of right eye from an age- and sex-matched subject with CKD. Note marked thinning of choroidal vascular lying underneath the retina.

Supplementary video 3. *OCT angiography of macula in health*

Video of sequential 'layer by layer' OCT angiograms centred on macula of right eye from a healthy volunteer. The track bar on the left-hand side relates colour-coded anatomic localisation of retinal regions that correspond to the angiograms shown in main panel.

Supplementary video 4. *OCT angiography of optic disc in health*

Video of sequential 'layer by layer' OCT angiograms centred on fundus of right eye from a healthy volunteer. The track bar on the left-hand side relates colour-coded anatomic localisation of retinal regions that correspond to the angiograms shown in main panel.

Supplementary information is available on Kidney International's web site

11. References

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