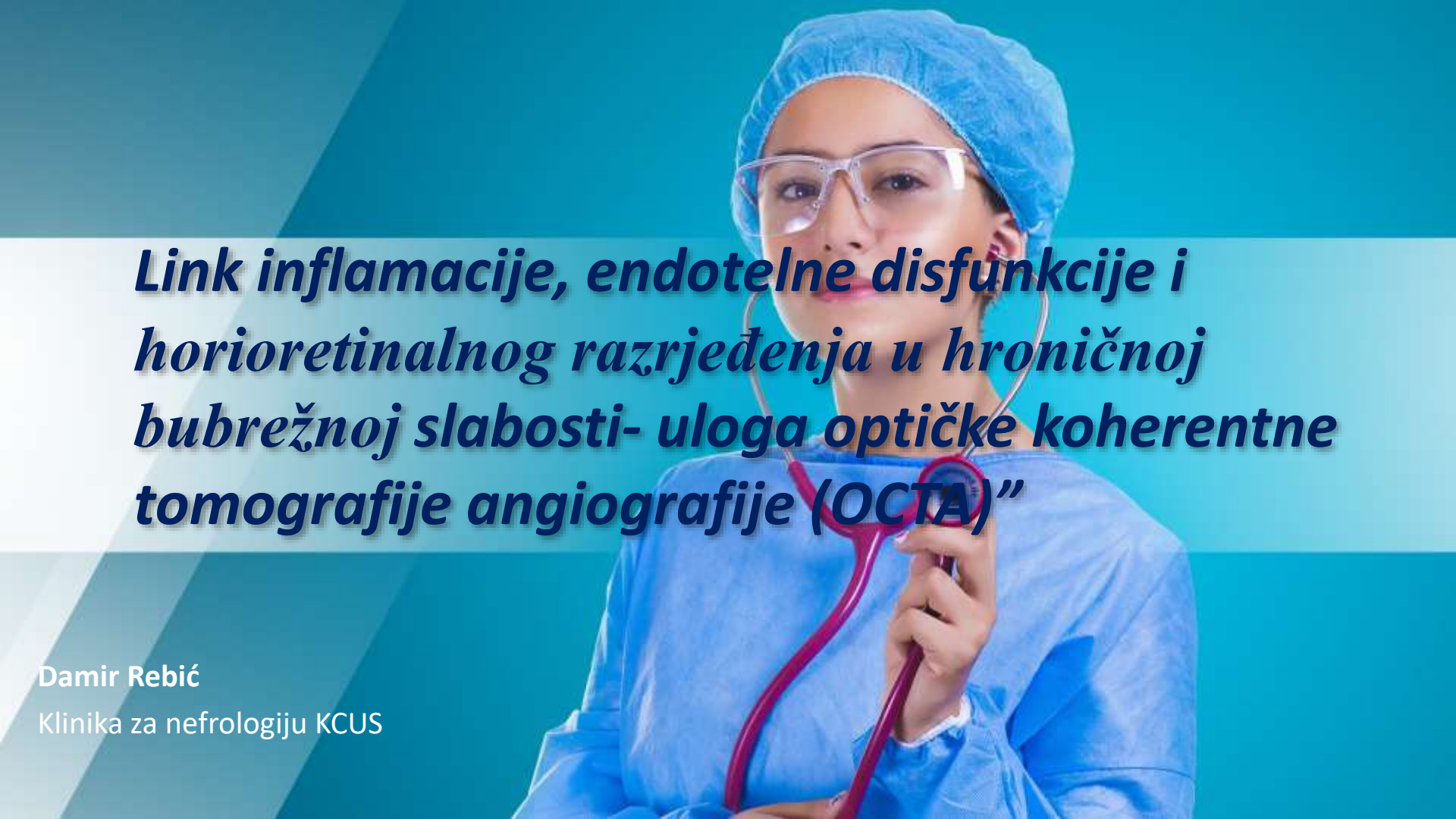


Link inflamacije, endotelne disfunkcije i horioretinalnog razrjeđenja u hroničnoj bubrežnoj slabosti- uloga optičke koherentne tomografije angiografije (OCTA)”

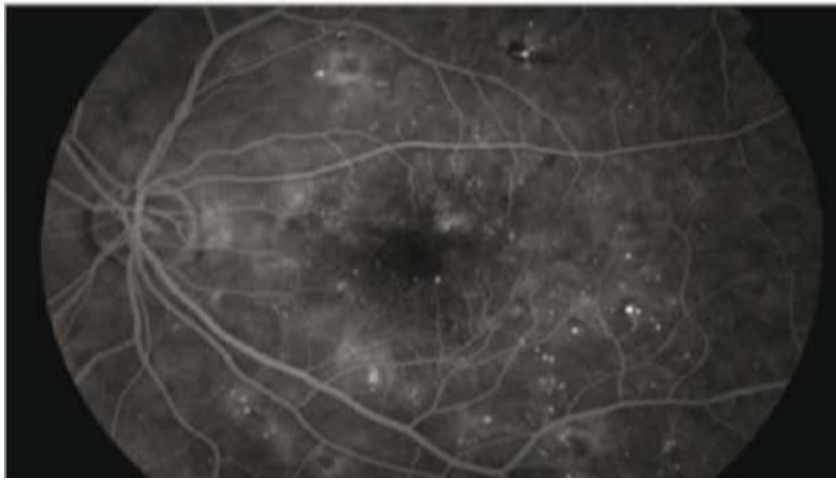
Damir Rebić

Klinika za nefrologiju KCUS

Link inflamacije, endotelne disfunkcije i horioretinalnog razrjeđenja u CKD-uloga OCTA

- CKD je snažno povezana sa incidentnim CVD
- Bubreg i oko su vrlo slični u razvojnim, strukturnim i patogenim putovima
- OCTA je nova, neinvanzivna metoda prikaza mikrovaskualrne cirkulacije retine i brzo otkrivanje lezija u parafovealnim kapilarima

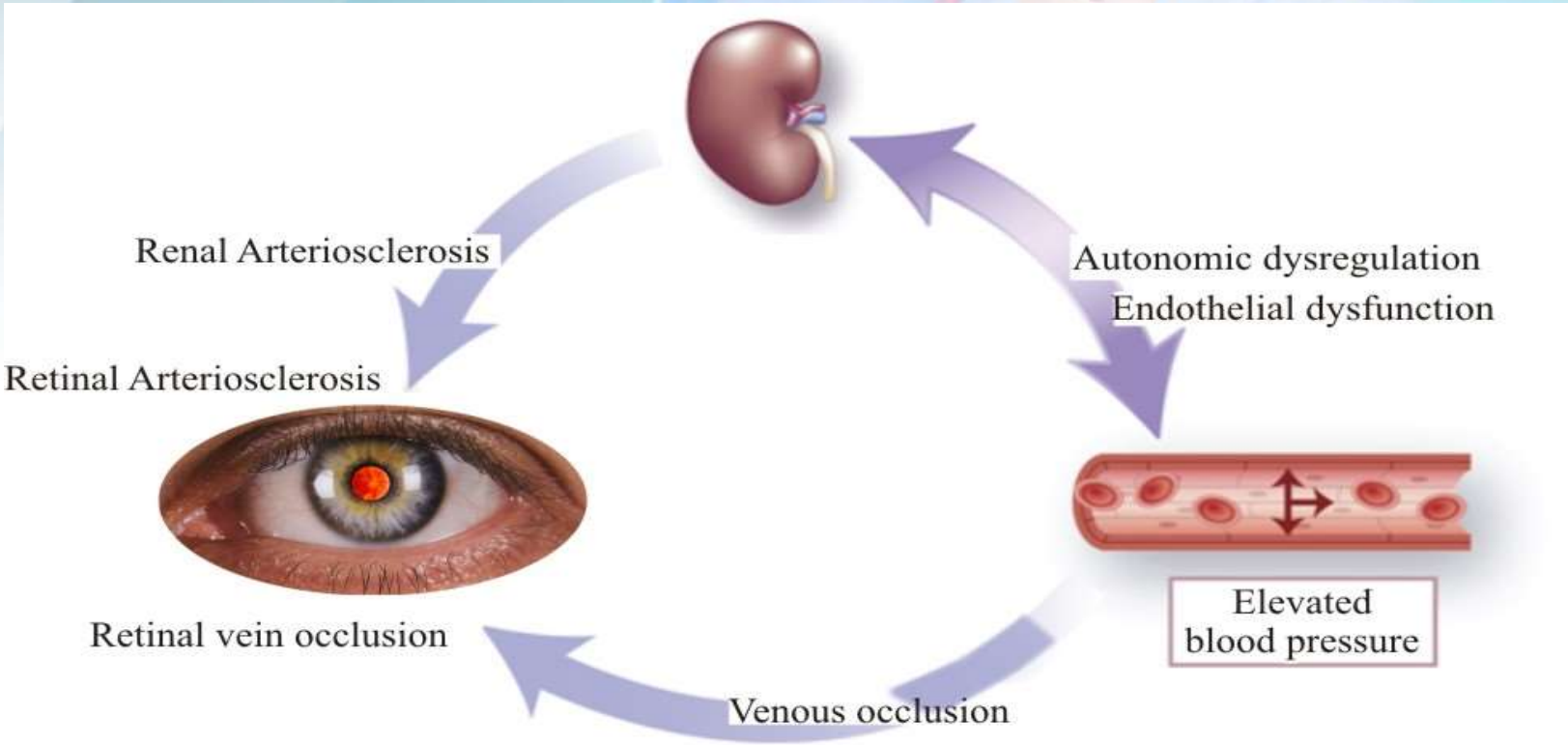
• OCTA imaging pokazuje strukturalne promjene unutar retine i choroida u bolesnika s hipertenzijom i CKD



• Endotelna disfunkcija i inflamacija kao etablirani riziko faktori za KVB u pozitivnoj su korelaciji sa mikrovaskularnim promjenama u bolesnika sa CKD

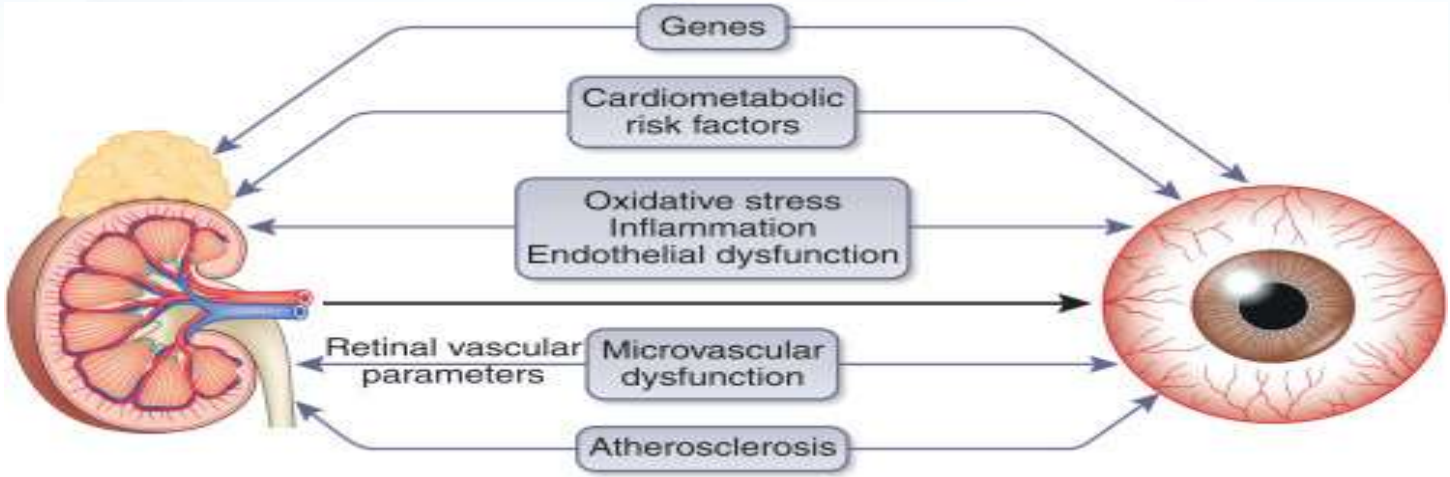
- Upotreba OCTA u CKD bolesnika s visokim rizikom CVD-a ostaje neistražena

Link inflamacije, endotelne disfunkcije i horioretinalnog razrjeđenja u CKD-uloga OCTA



Common pathogenetic mechanisms underlying renal and retinal diseases

Mechanisms of CKD	Associated eye diseases
Atherosclerosis	Cataract, AMD, DR, glaucoma, retinal vascular damage
Endothelial dysfunction	AMD, cataract
Oxidative stress	Cataract, DR, AMD, glaucoma, retinal vascular damage
Inflammation	AMD, DR, retinal vascular damage
Renin–angiotensin system dysfunction	DR, retinal vascular damage, glaucoma
Genetic polymorphisms	AMD, retinal venular diameter
Klotho	AMD, cataract, retinopathy



Kidney International 2014 85, 1290-1302DOI: (10.1038/ki.2013.491)

Common risk factors shared between CKD and eye diseases

Risk factors of CKD	Associated eye diseases
Age	Cataract, AMD, DR, glaucoma, retinal vascular damage
Smoking	AMD, cataract
Diabetes mellitus	Cataract, DR, AMD, glaucoma, retinal vascular damage
Hypertension	AMD, DR, retinal vascular damage, glaucoma
Obesity	AMD, DR, cataract
Hyperlipidemia	AMD, DR

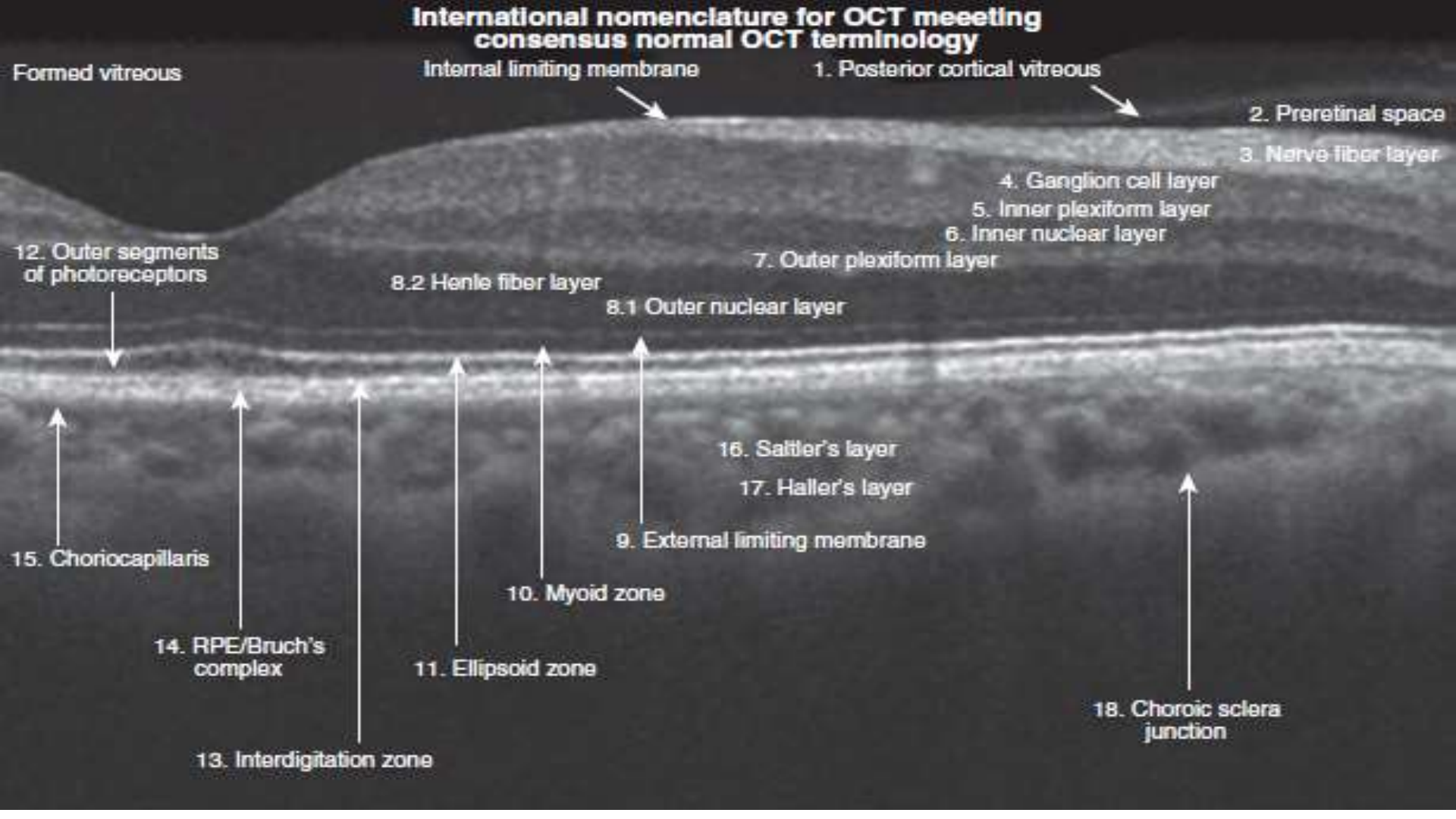
Abbreviations: AMD, age-related macular degeneration; CKD, chronic kidney disease; DR, diabetic retinopathy.

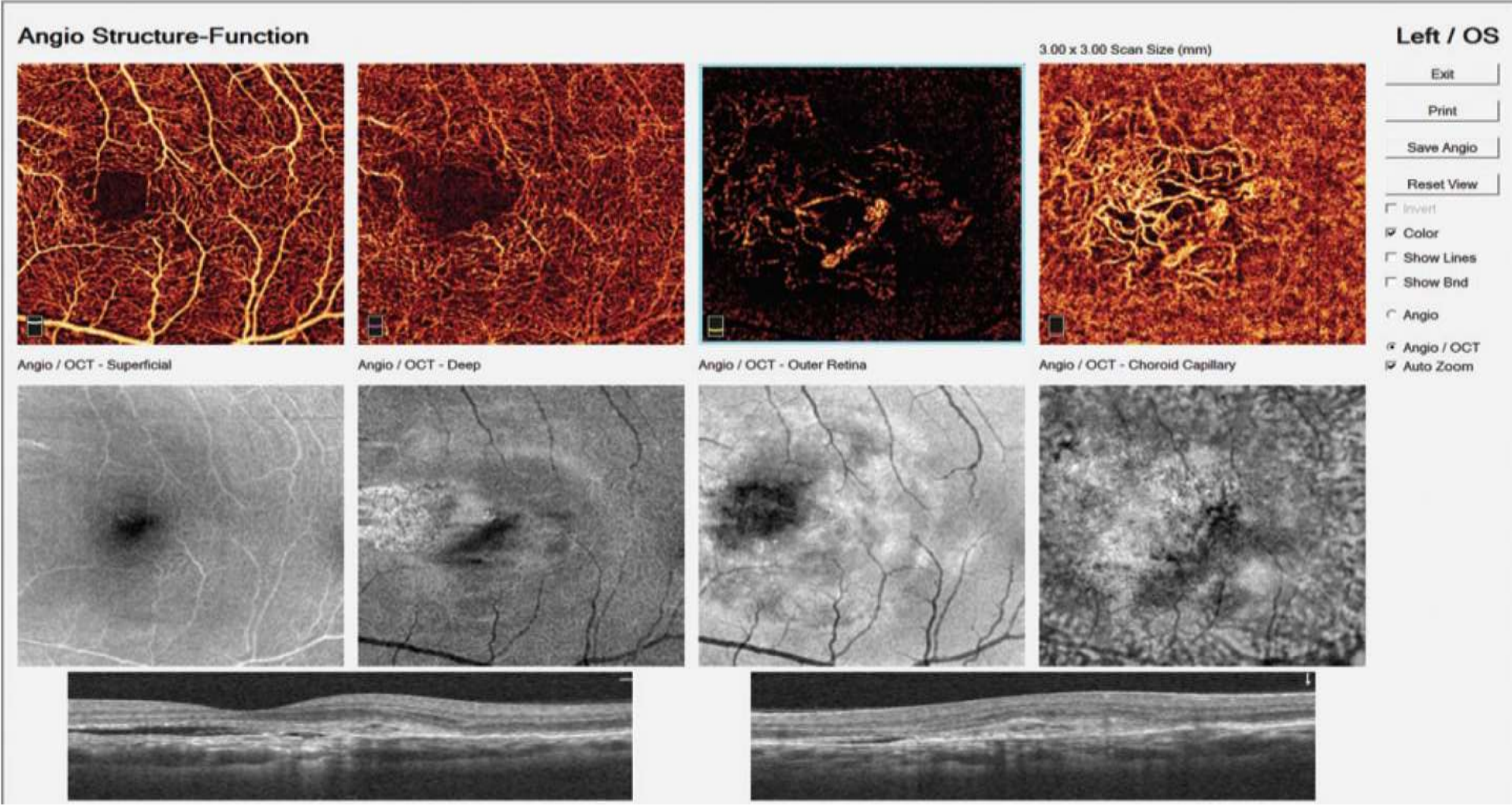
Kidney International **2014 85, 1290-1302DOI: (10.1038/ki.2013.491)**

Udruženost vaskularnih promjena retine i CKD

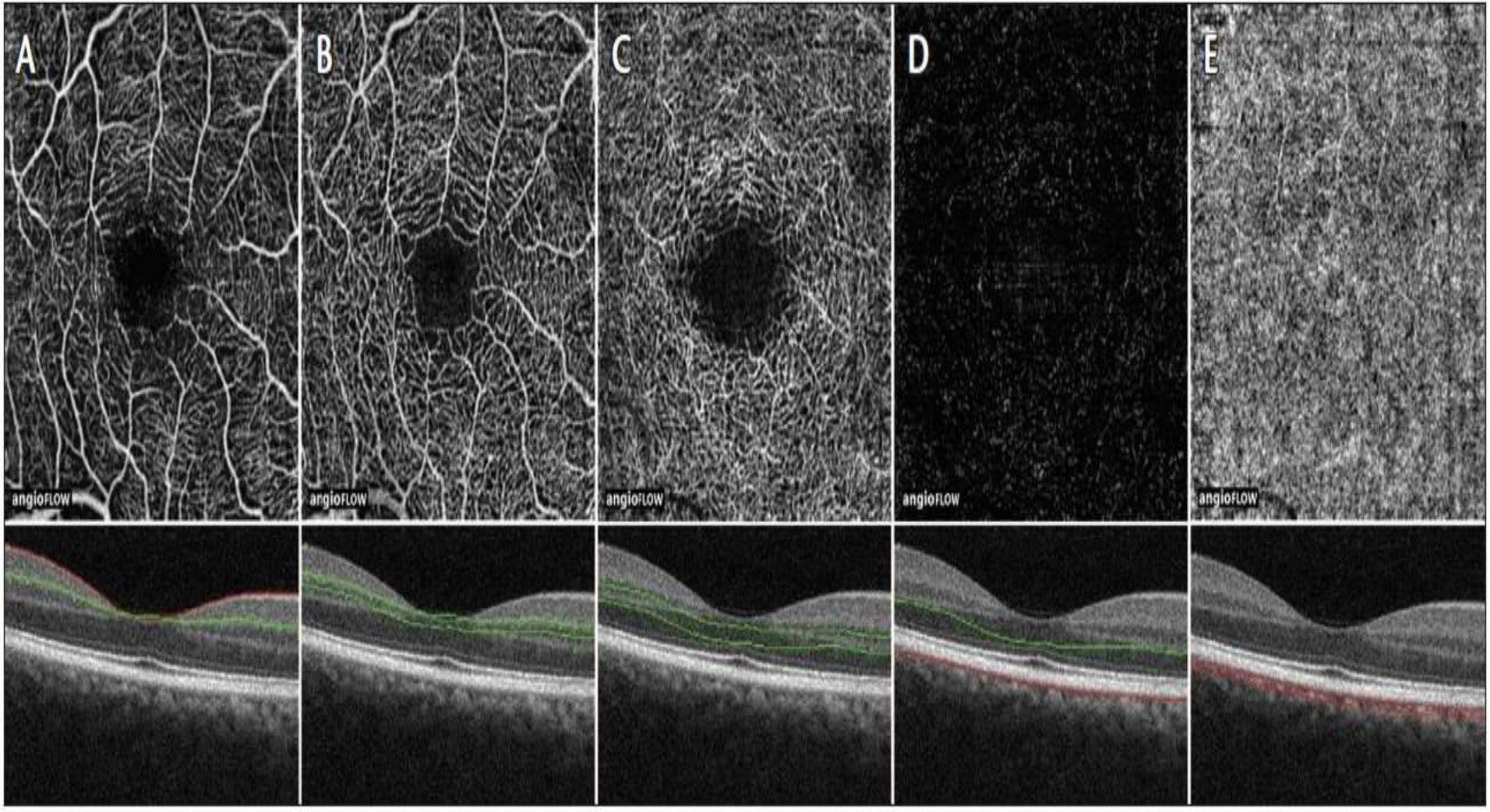
Author, year	Type of study and location	Sample size	Retinal vascular measure	Definition of CKD	Results
Risk of retinal vascular changes in individuals with/without CKD					
Liew et al., 2012[117]	Population-based cross-sectional study (BMES), Australia	n=2971	CRVE	eGFR <60ml/min per 1.73m^2	CKD was associated with the presence of retinal venular (CRVE) dilation,
Myers et al., 2012[153]	Population-based prospective study (BDES), Wisconsin, USA, follow-up=15 years	n=4600	CRVE	eGFR <45ml/min per 1.73m^2	CKD was associated with a greater decrease in CRVE over time
Ooi et al., 2011[138]	Hospital-based case–control study, CKD stage 3–5 vs. CKD stage 1–2, Australia	Cases: 126, controls: 126	CRAE, CRVE	eGFR <60ml/min per 1.73m^2	Patients with CKD stage 3–5 had a smaller mean CRAE and CRVE than hospital controls
Sabanayagam et al., 2011[145]	Population-based prospective study (BDES) of adults aged 43–84 years, Wisconsin, USA, follow-up=15 years	n=3199	CRAE, CRVE	eGFR <60ml/min per 1.73m^2 accompanied by a 25% decrease in eGFR, during follow-up	Baseline eGFR was not associated with 15-year risk of incident retinal arteriolar narrowing or retinal venular widening
Risk of CKD in individuals with/without retinal vascular changes					
Yau et al., 2011[144]	Population-based prospective study (MESA) of whites, African-Americans, Chinese, and Hispanics aged 45–84 years, USA, follow-up=5 years	n=4594	CRAE, CRVE	eGFR <60ml/min per 1.73m^2	CRAE was associated with incident CKD stage 3 in whites only. comparing lowest with highest CRAE tertile
Sabanayagam et al., 2011[145]	Population-based prospective study, adults aged 43–84 years, BDES, Wisconsin, USA, follow-up=15 years	n=3199	CRAE, CRVE	eGFR <60ml/min per 1.73m^2 accompanied by a 25% decrease in eGFR, during follow-up	Baseline CRAE and CRVE were not associated with 15-year risk of incident CKD

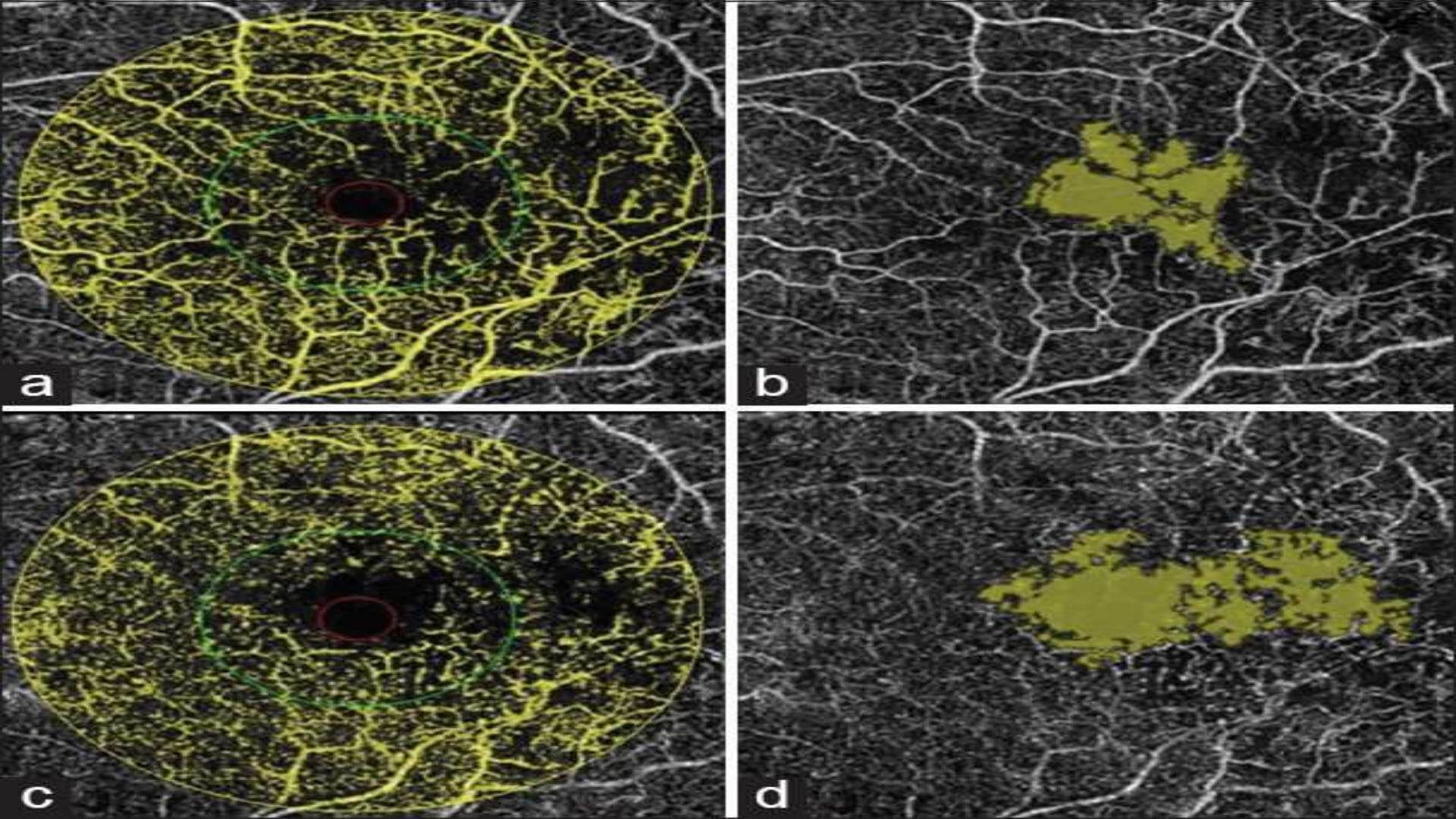
Kidney International **2014 85, 1290-1302DOI: (10.1038/ki.2013.491)**


International nomenclature for OCT meeeting consensus normal OCT terminology
Formed vitreous
Internal limiting membrane
1. Posterior cortical vitreous
2. Preretinal space
3. Nerve fiber layer
4. Ganglion cell layer
5. Inner plexiform layer
6. Inner nuclear layer
7. Outer plexiform layer
8.2 Henle fiber layer
8.1 Outer nuclear layer
12. Outer segments of photoreceptors
16. Saltler's layer
17. Haller's layer
9. External limiting membrane
15. Choriocapillaris
10. Myoid zone
14. RPE/Bruch's complex
11. Ellipsoid zone
13. Interdigitation zone
18. Choroic sclera junction

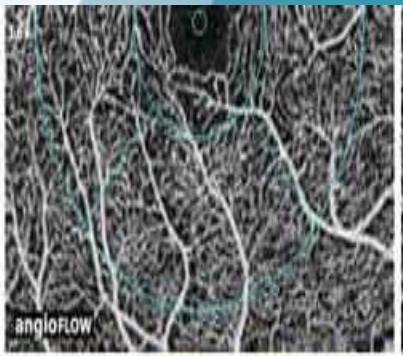


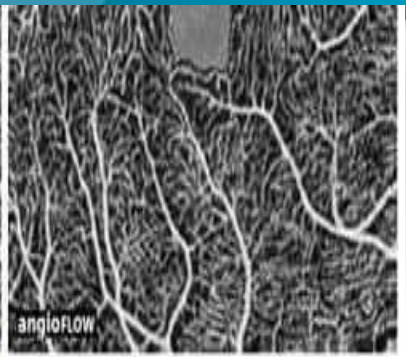
OCTA površne i duboke vaskularne mreže zdravog oka 3x3mm; Vide se paučinasto raspoređeni kapilari koji tvore mrežu oko koncentrične centralne avaskularne zone

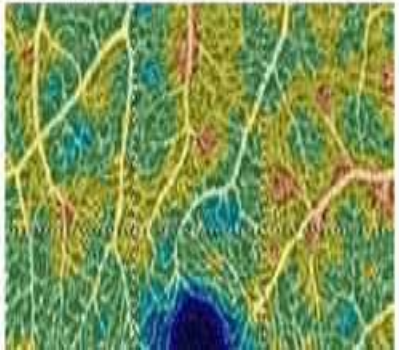

A
B
C
D
E
angioFLOW
angioFLOW
angioFLOW
angioFLOW
angioFLOW


a
b
c
d

Flow density map

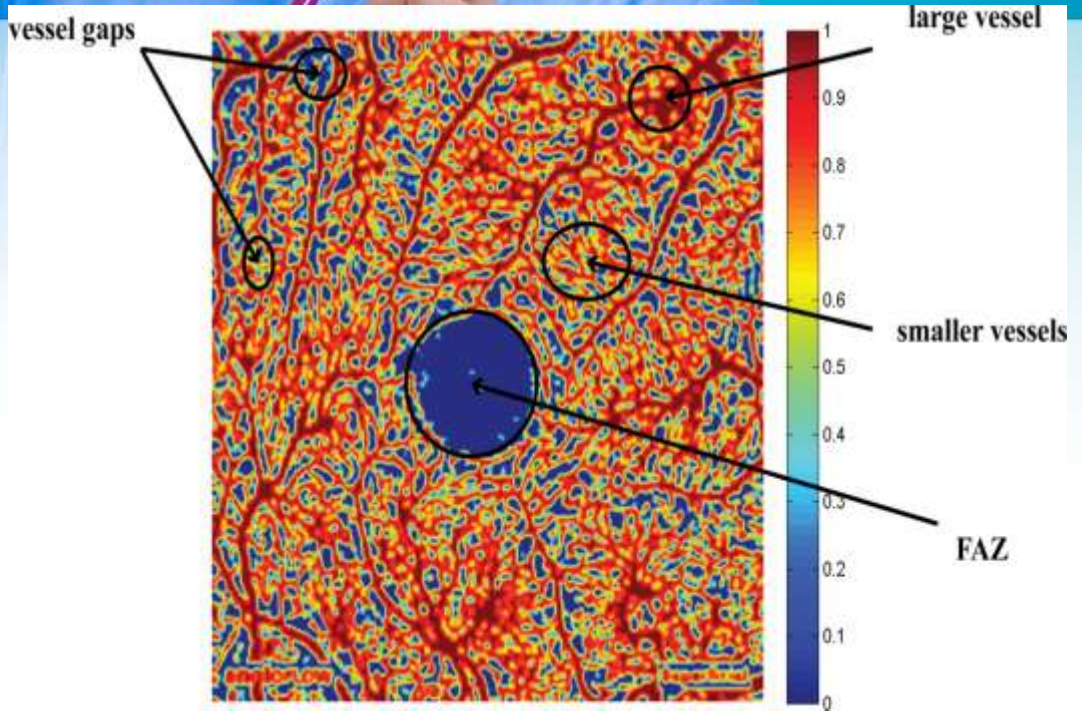




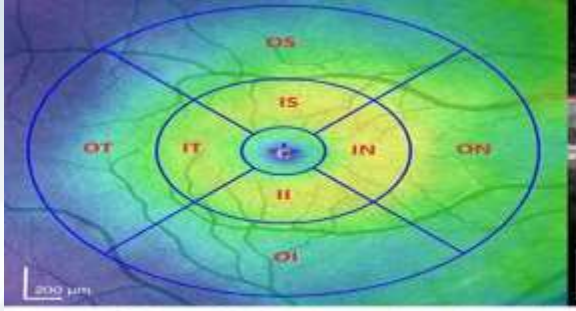


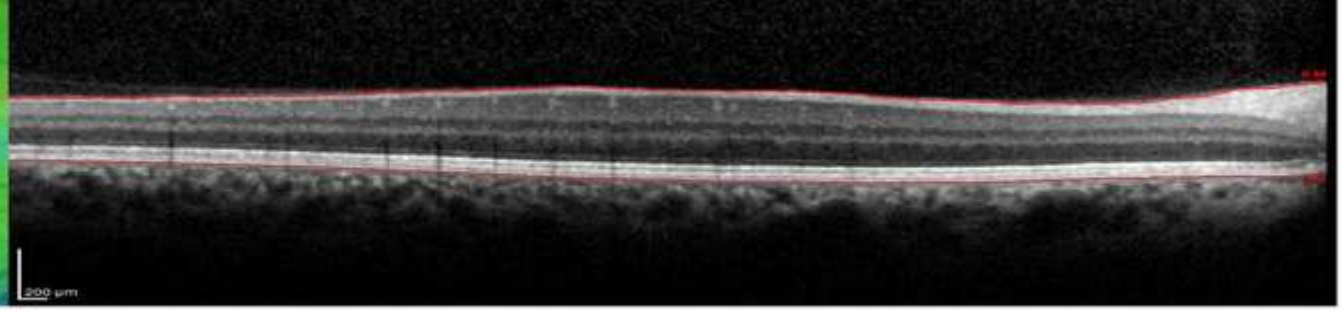
OCT Thickness ILM-RPE & Flow Density

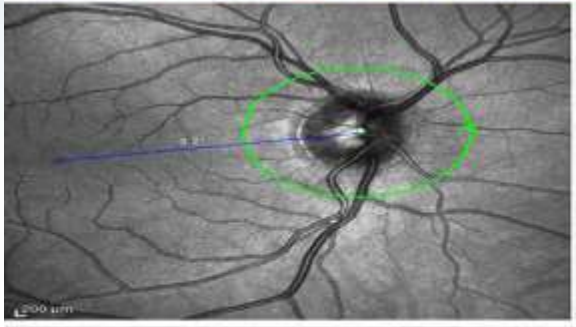
Section	Thickness (µm)	Density (%)
Whole en face	N/A	54.20
Fovea	285	33.65
ParaFovea	332	56.01

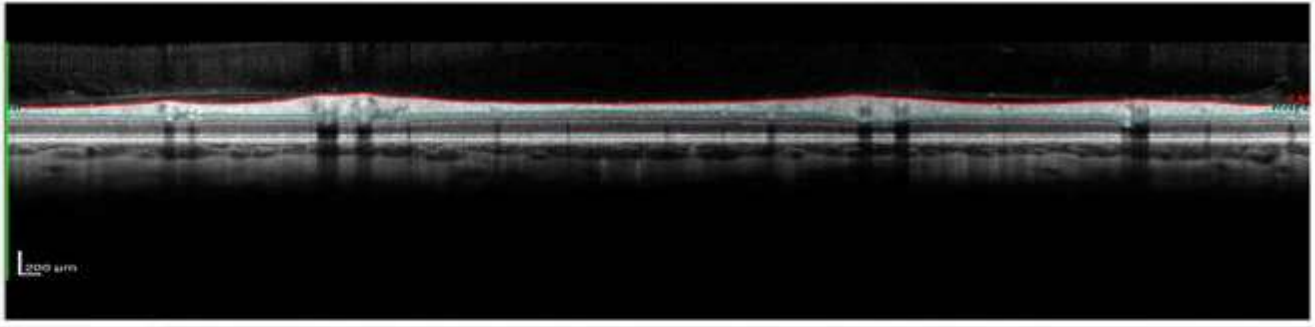


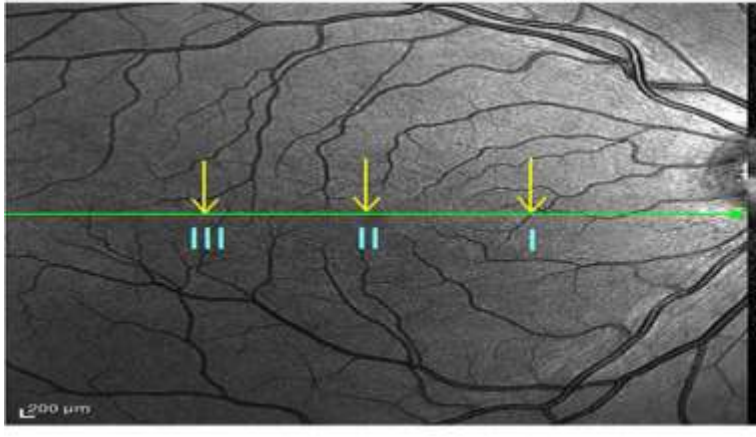
Leitgeb RA, Werkmeister RM, Blatter C, Schmetterer L. Doppler optical coherence tomography. *Prog Retin Eye Res. 2014;41:26–43*.

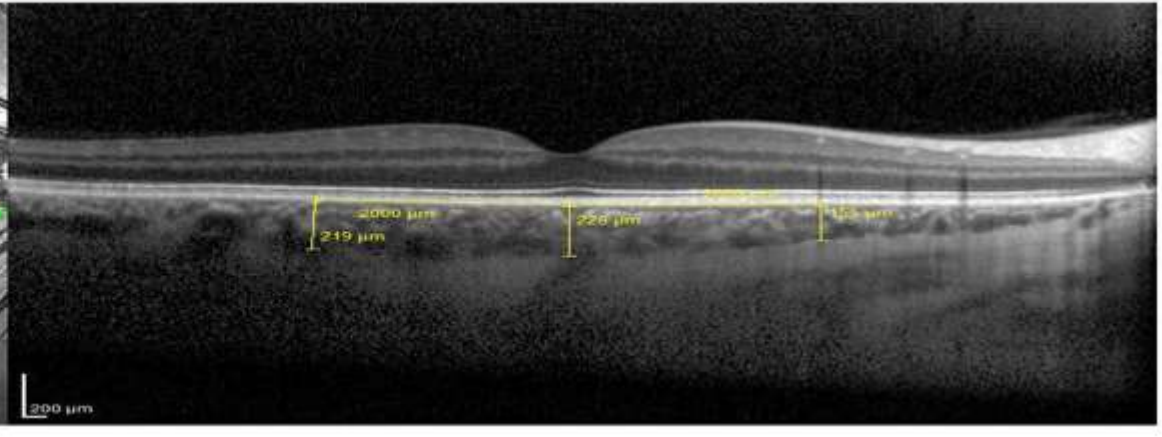

OS
IS
OT
IT
IN
ON
II
OI
200 µm

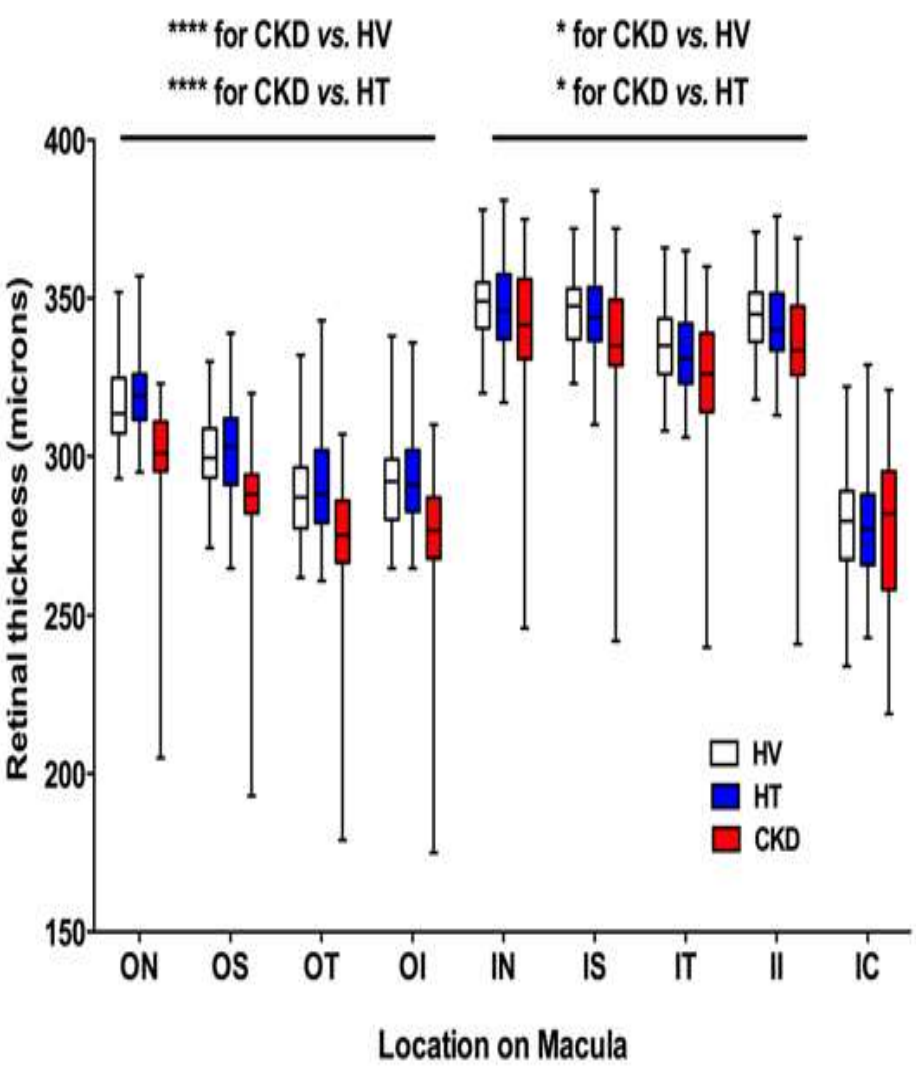

200 µm

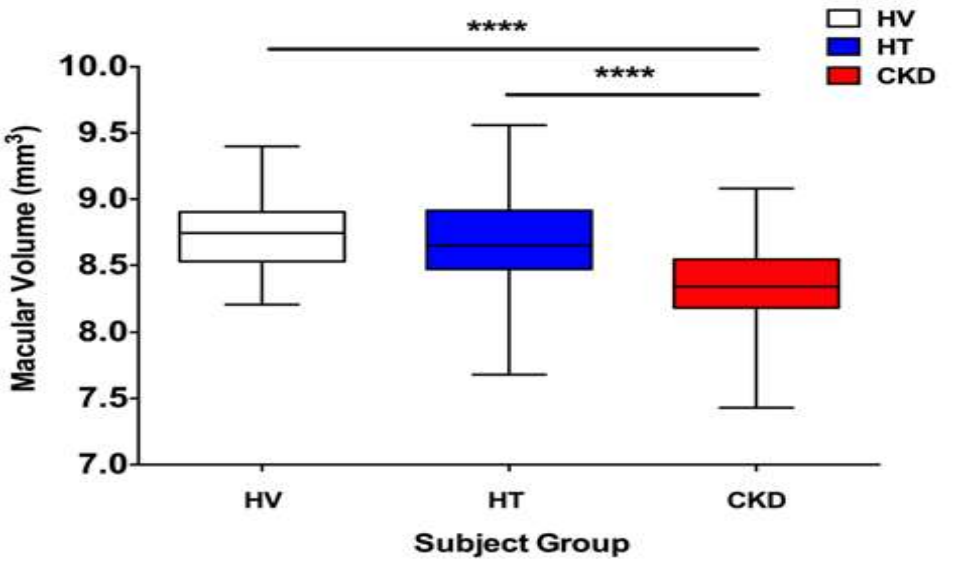

200 µm


200 µm

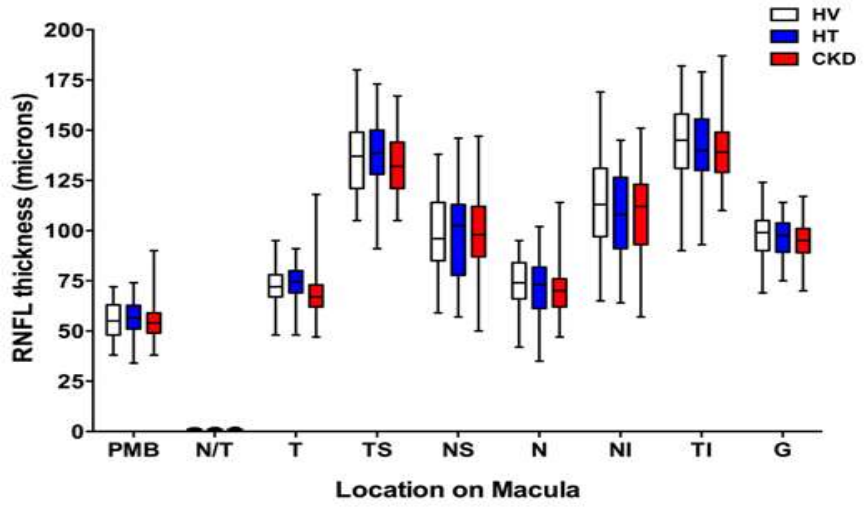

III
II
I
200 µm

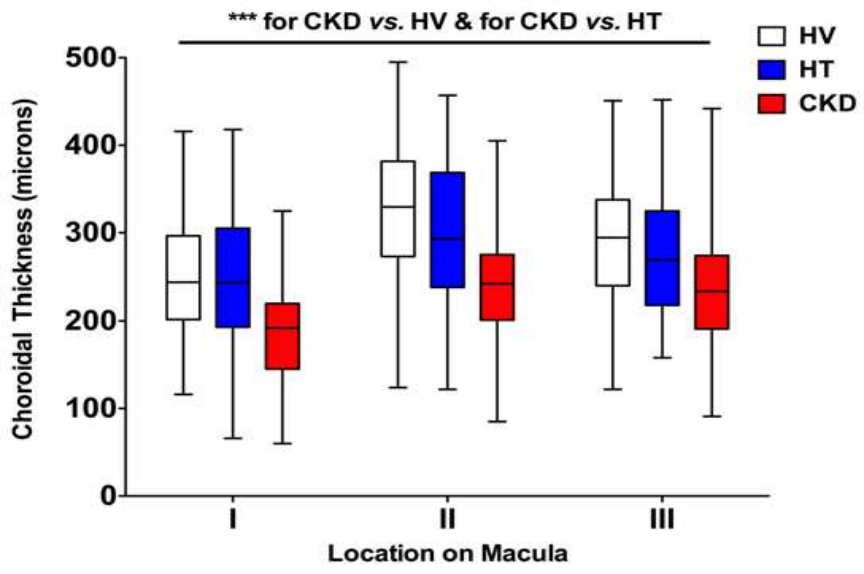

2000 µm
219 µm
226 µm
200 µm

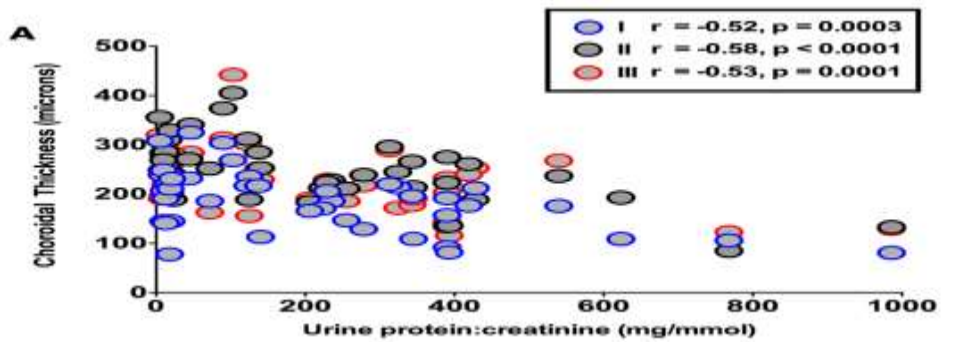


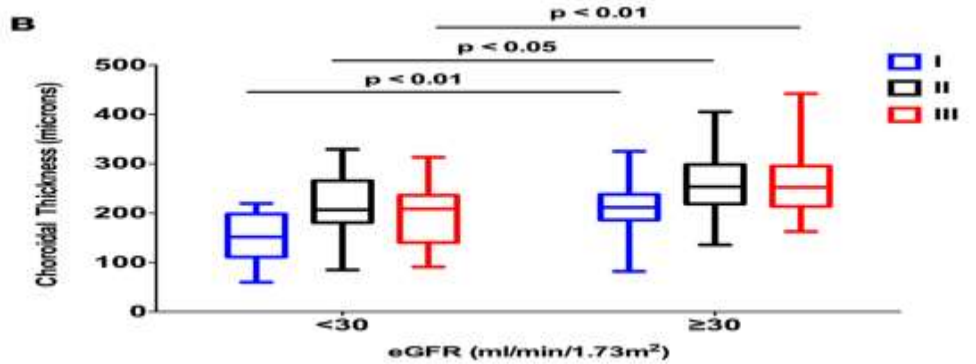


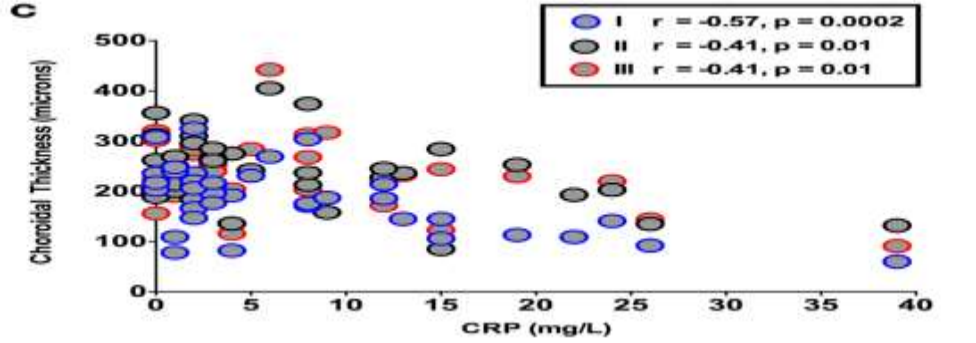
Balmforth C, JCI Insight. 2016 Dec 8;1(20):e89173.

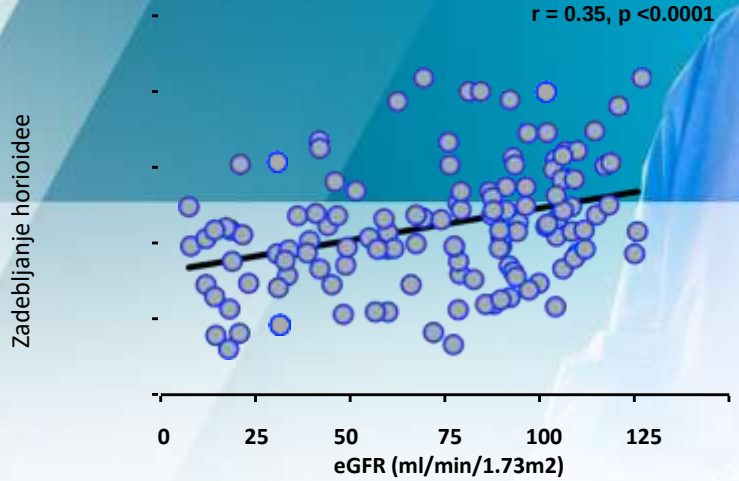

HV
HT
CKD
RNFL thickness (microns)
200
175
150
125
100
75
50
25
0
PMB
N/T
T
TS
NS
N
NI
TI
G
Location on Macula

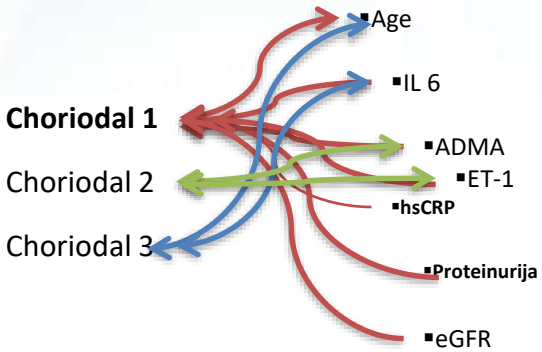

*** for CKD vs. HV & for CKD vs. HT
HV
HT
CKD
Choroidal Thickness (microns)
500
400
300
200
100
0
I
II
III
Location on Macula


A
I r = -0.52, p = 0.0003
II r = -0.58, p < 0.0001
III r = -0.53, p = 0.0001
Choroidal Thickness (microns)
500
400
300
200
100
0
0
200
400
600
800
1000
Urine protein:creatinine (mg/mmol)


B
p < 0.01
p < 0.05
p < 0.01
I
II
III
Choroidal Thickness (microns)
500
400
300
200
100
0
<30
≥30
eGFR (ml/min/1.73m²)

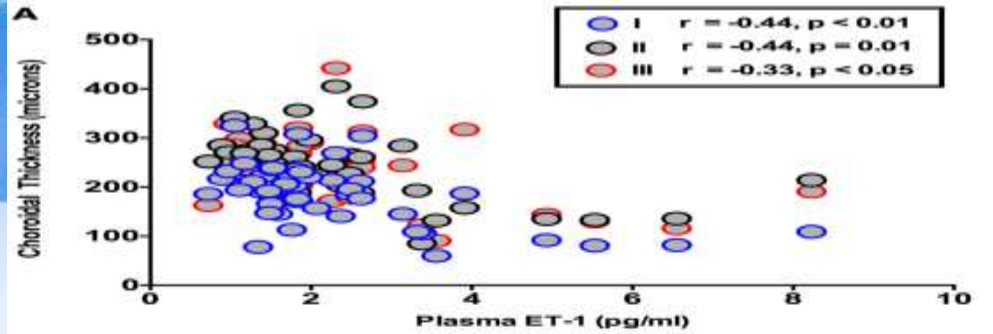

C
I r = -0.57, p = 0.0002
II r = -0.41, p = 0.01
III r = -0.41, p = 0.01
Choroidal Thickness (microns)
500
400
300
200
100
0
0
5
10
15
20
25
30
35
40
CRP (mg/L)

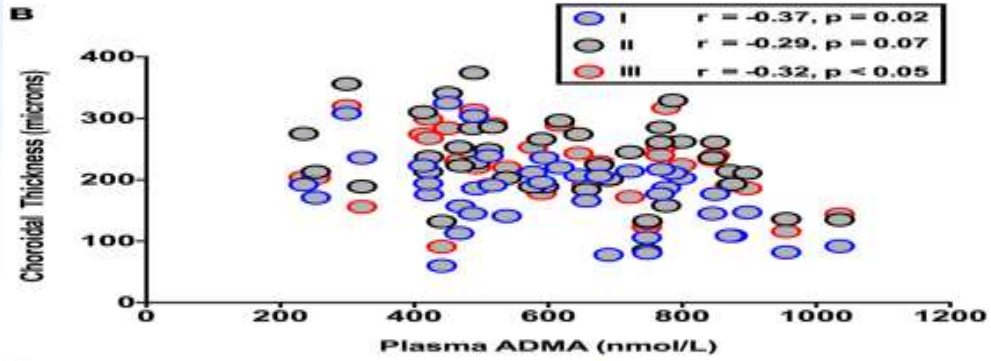


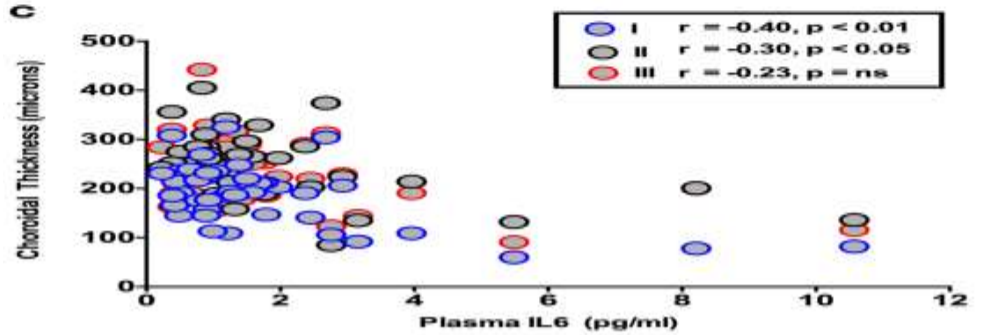


Component 2; 3 (14.18%)

Component 1 (43.29%)







Plasma measure	Healthy (n = 50)	Hypertensive (n = 50)	CKD (n = 50)
IL-6, pg/ml	0.78 ± 0.43A	1.66 ± 2.11	1.87 ± 2.08
TNF-α, pg/ml	1.01 ± 0.73	1.08 ± 0.74	2.16 ± 1.09B
ET-1, pg/ml	1.39 ± 0.8	1.72 ± 0.69	2.29 ± 1.50C
ADMA, nmol/l	295 ± 129	327 ± 160	624 ± 202B

Parameter	Choroidal Location[A]		
	I	II	III
Age	–0.06	–0.12	–0.32B
hsCRP	–0.46B	–0.28B	–0.22
Urine P:Cr	–0.29B	–0.43B	–0.50B
IL-6	–0.45B	–0.29B	–0.22
ET-1	–0.11	–0.05	–0.13
ADMA	–0.19	–0.15	–0.21
r^2	0.68	0.49	0.38

Balmforth C, JCI Insight. 2016 Dec 8;1(20):e89173.

ZAKLJUČAK

- *Postoje znatni dokazi o uskoj povezanosti bolesti bubrega i očiju*
- *Mikrovaskularne promjene, poput retinopatije su prediktivne za CKD*
- *Razumijevanje patofiziologije bolesti u bubregu i oku omogućiti će razvoj novih strategija liječenja oboljenja bubrega i očiju.*
- *Kvantifikacija mikrovaskularnih promjena retine OCTA može omogućiti razvoj biomarkera za CKD*
- ***Bilo bi od velike kliničke vrijednosti ako se retinalni OCTA-rezultati koriste za otkrivanje i praćenje vaskularne ozljede unutar oka u ranoj fazi i kao surogat mjera bubrežne vaskularne ozljede.***

ZAKLJUČAK

- *Veći protok u SCP, I pad u DCP (procjenjen OCTA) može biti rani marker dijabetičkih mikrovaskularnih promjena prije kliničkih znakova generalizirane ateroskleroze karakteristične za CKD.*

- *Upala i endotelna disfunkcija, uz CKD povećava rizik od CVD sa manifestnim horiretinalnim razrjeđenjem vaskularnog pleksusa*

Quantifying Microvascular Abnormalities of Diabetics in Chronic Kidney Patients

Methods

- A prospective cross-sectional study in 40 eyes of 24 diabetics with different stages of CKD and diabetic retinopathy
- OptoVue OCTA machine, AngioVue system to examine:
  superficial and deep capillary plexuses (SCP and DCP) on macular OCTA scans (3 × 3mm) centered on the fovea

- ***Qualitative analysis***

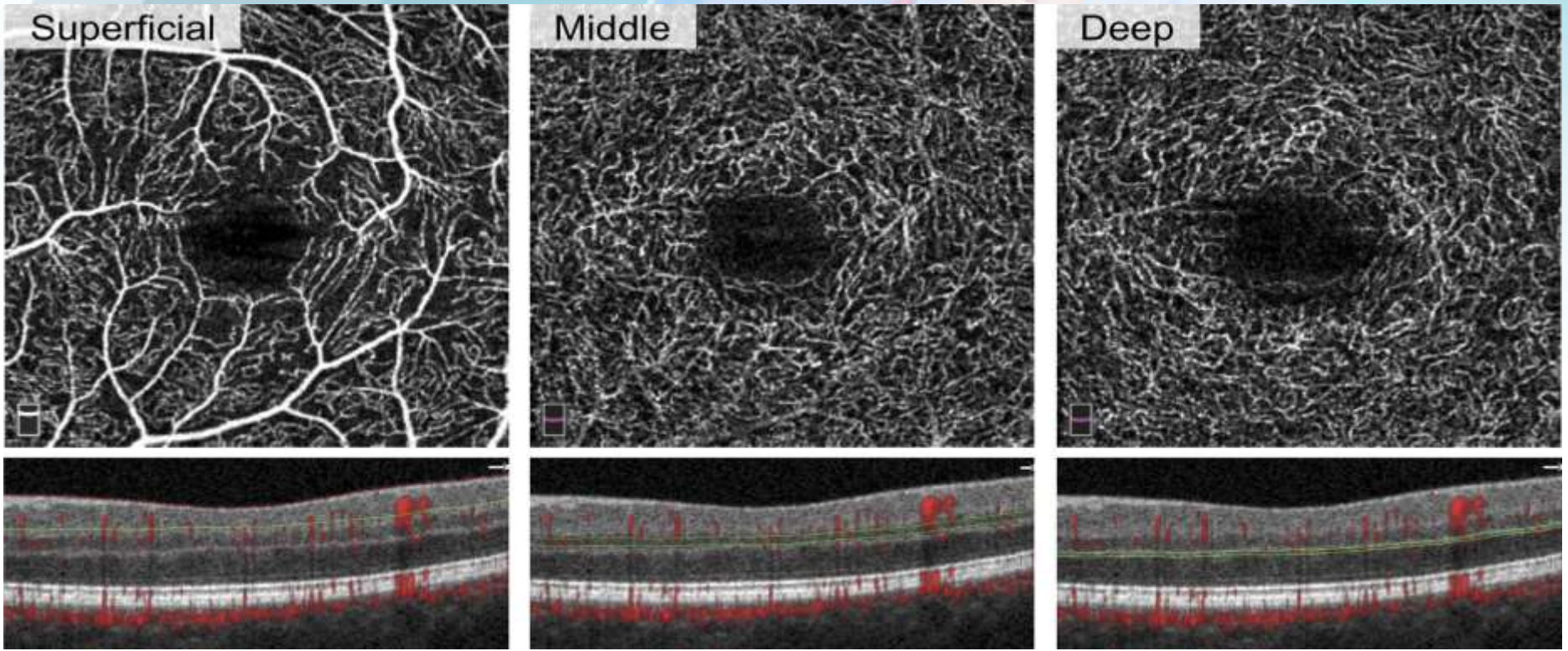
(morphological ischemic capillary alterations)

- ***Quantitative analysis***

a. foveal avascular zone (FAZ) size,
b. parafoveal capillary density,
c. microaneurysms,
d. neovasularisations,
e. percent area of nonperfusion (PAN),
f. adjusted flow index (AFI).

Endothelial function and inflammation (CRP, NO, ET-1)

Quantifying Microvascular Abnormalities of Diabetics in Chronic Kidney Patients



Segmentation of three capillary plexuses on OCTA. Left eye of patient with DM without DR. En face (top row) and cross-sectional (bottom row) OCTA of the superficial (left), middle (center), and deep (right) capillary plexuses. The red and green lines on cross-sectional OCTA show the segmentation boundaries for each layer.

Quantifying Microvascular Abnormalities of Diabetics in Chronic Kidney Patients

Demographic and Disease-Related Patient Characteristics

	Healthy controls	DM without CKD	DM with eGFR 30-60ml/min	DM with eGFR<30ml/min	P value
Patients, n	8	8	12	12	
Eyes, n	16	16	23	17	<0.01
Sex, m/f	3/5	6/2	4/8	6/6	0.05
Age, years, mean	50	47	59	61	0.62
Disease, duration, years mean	N/A	8	10	11	
Arterial hypertension, yes	3	3	6	9	
Dyslipidemia, yes	0	5	6	6	
Smoker, yes	3	7	2	8	
BMI ((kg/m^2)	25.9±3.7	27.2±2.5	27.8±5.2	26.1±4.6	0.197
IMT CCA ((mm)	0.65 (0.55-0.6	0.73 (0.6-0.9)	0.92 (0.8-1.0	0.96 (0.9-1.1)	<0.01
NO (µmol/L)	92.72 (21.4-136.7)	80.2 (12.7-96.8)	52.34 (13.8-65.2)	40.72 (19.4-56.7)	<0.01
ET-1 (pg/mL)	1.39 ± 0.80	1.72 ± 0.69	2.29 ± 1.50	6.32 ± 3.20	<0.01
CRP (mg/L)	4.5 (<3-5,4)	9.2 (6.6-12.8)	11.5 (5.5-21.2)	11.1(6.1-16.4)	
HbA1c	N/A	7,4	7,0	8,1	
Lens status					
Clear	8	6	2		
Cataract		2	9	9	
Pseudophakie	0	0	1	3	

Quantifying Microvascular Abnormalities of Diabetics in Chronic Kidney Patients

Intima-media thickness of CCA and concentrations of NO, ET-1, and CRP in subjects with Disease-Related Patient Groups (mean ± SD)

	Healthy controls	*DM without CKD*	*DM with eGFR 30-60ml/min*	*DM with eGFR<30ml/min*	*P value*
IMT CCA (mm)	0.57 ±0.1	0.68 ±0.1	0.92 ±0.2	0.94±0.2	<0.01
NO (µmol/L)	63.2(59.7-106.2)	38.5 (14.8-46.8)	52.4 (49.4-99.1)	36.2 (21.7-49.2)	<0.05
ET-1 (pg/mL)	2.6(2.2-4.0)	7.0 (4.1-8.8)	6.2 (2.0-7.5)	8.7 (4.0-9.4)	<0.05
CRP (mg/L)	5.7±3.5	13.9±8.4	2.6±1.3	6.4±2.9	<0.01
tHcy (µmol/L)	14.8 (12.2-16.7)*	20.1 (18.2-23.0)	26.6 (21.6-31.4)	25.2 (20.2-30.1)	<0.01

Quantifying Microvascular Abnormalities of Diabetics in Chronic Kidney Patients

Outcome Measures	*Healthy controls*	*DM without CKD*	*DM with eGFR 30/60ml/min*	*DM with eGFR<30ml/min*	*Spearman R value*	*Pearson P value*
FAZ mm²						
SCP	0.266±0.073	0.302±0.144	0.365±0.199	0.483±0.218	0.403*	<0.01*
Full retina	0.255±0.073	0.311±0.148	0.353±0.188	0.469±0.223	0.362*	<0.01
coefficient of enlargement of FAZ	0.27 ± 0.7	0.26± 0.5	0.43 ± 0.32	0.60 ± 0.61	-0.145*	0.07
Vessel density %						
SCP	52.3±2.89	53.01±3.07	48.48±3.55	42.12±1.28	-0.646*	<0.01*
DCP	60.62±1.96	58.24±2.6	52.86±4.46	49.44±3.88	-0.786*	<0.01*
Full	57.28±2.24	57.02±3.36	52.64±5.28	46.58±5.6	-0.602*	<0.01*
Microaneurysms, %, (>10)	0	25	41,6	66.6		
Cotton wool yes/no	0/8	2/6	4/8	9/3		
Neovascularisation yes/no	0/8	1/7	3/9	7/5		
PAN %						
SCP	12.44±2.25	15.03±4.46	21.3±4.91	25.59±4.12	0.649*	<0.01*
DCP	8.88±2.69	10.76±4.02	18.2±5.63	24.97±7.55	0.697*	<0.01*
Full	8.2±3.12	10.3±3.2	17.22±4.47	21.09±5.66	0.699*	<0.01*
CC	2.53±0.66	3.1±1.32	2.9±2.9	3-82±1.92	0.314*	<0.05†
AFI mean						
SCP	0.27±0.03	0.29±0.02	0.27±0.03	0.26±0.02	-0.107†	0.08
DCP	0.3±0.03	0.29±0.04	0.27±0.04	0.26±0.03	-0.401*	<0.01*
Full	0.31±0.03	0.32±0.03	0.29±0.04	0.29±0.03	-0.212*	<0.05†
CC	0.4±0.02	0.39±0.02	0.38±0.03	0.38±0.03	-0.206*	<0.05†
Retinal foveal thickness µm SD-OCT	277 ± 44	265±48	259±26	257 ± 34	-0.692*	<0.01*
Chorioidal subfoveal thickness µm SD-OCT	294 ± 68	278±56	269±52	264 ± 64	-0.497*	<0.01*

Univariate Correlations Between OCTA Parameters and Severity of CKD

*Correlation is significant at the 0.01 level (2 tailed)
†Correlation is significant at the 0.05 level (2 tailed)

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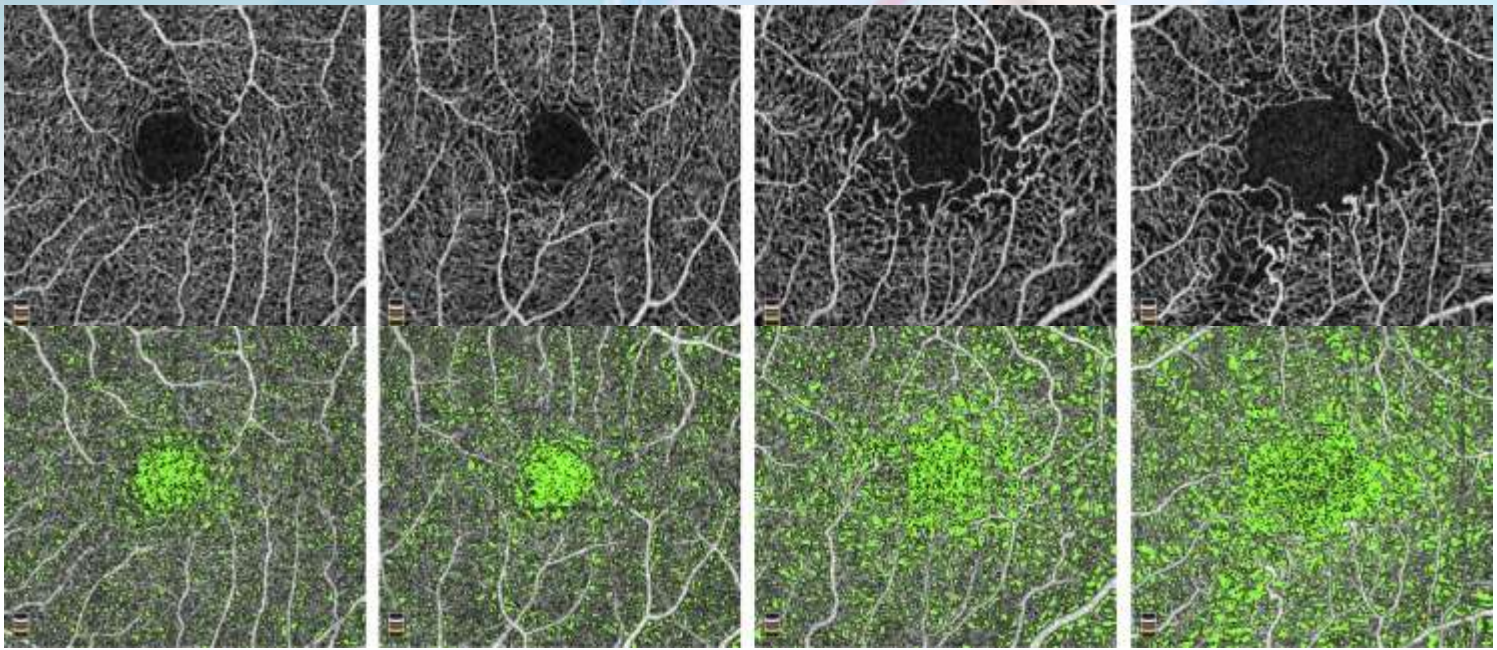
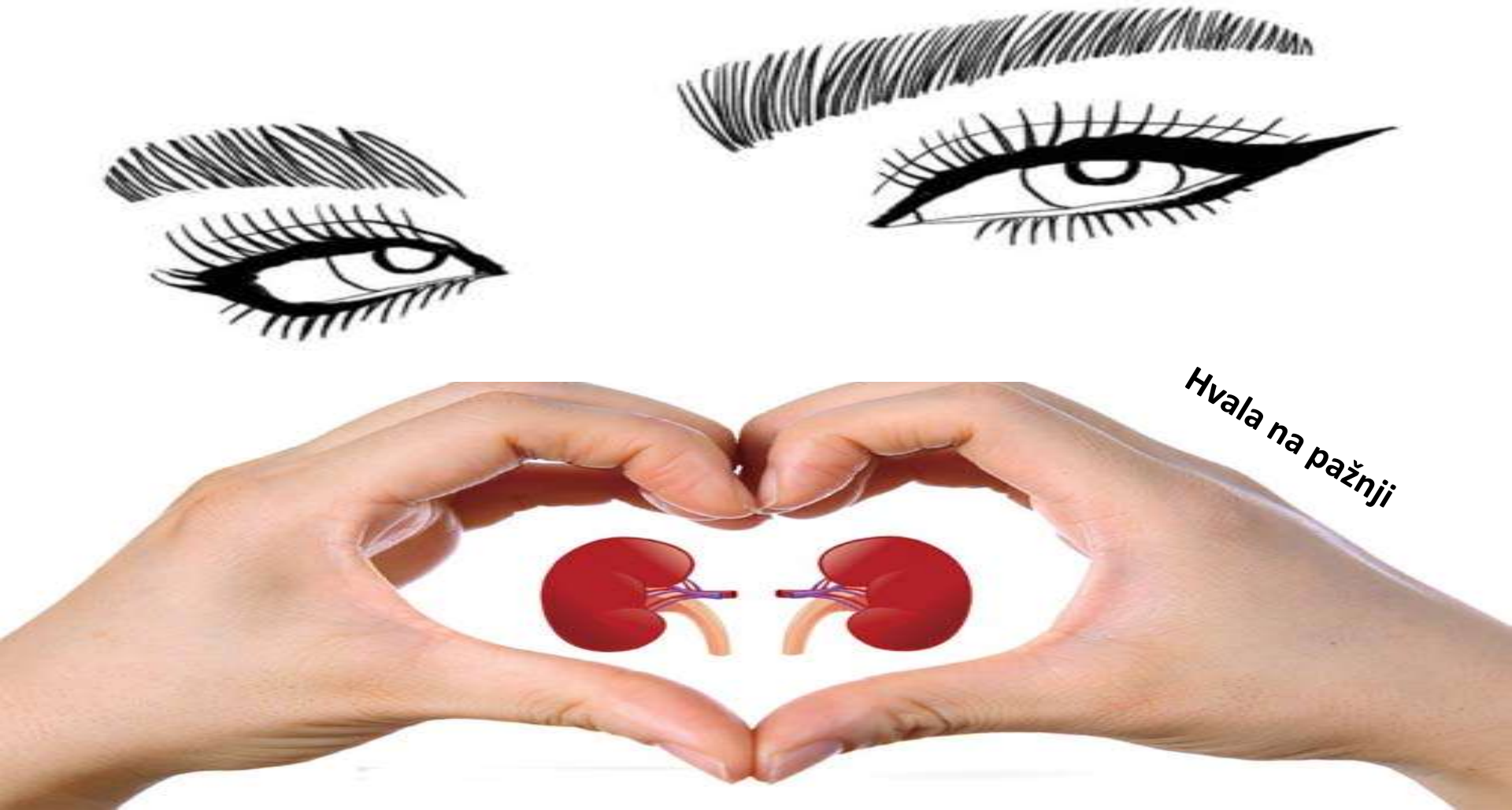


Vessel density decreases and PAN increases with increasing disease severity. Top Row: En face OCTA of full retinal thickness angiograms for a healthy patient (left), a patient with diabetes without CKD (middle left), a patient with CKD eGFR>60ml/min (middle right), and eGFR<60ml/min (right). Bottom Row: Areas of nonperfusion are shown in green. PAN is reported as a percentage of the area of nonperfusion to the total retinal area and increases from left to right.



Hvala na pažnji