Comparing Asian and Scottish Retinal Vasculature

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Introduction

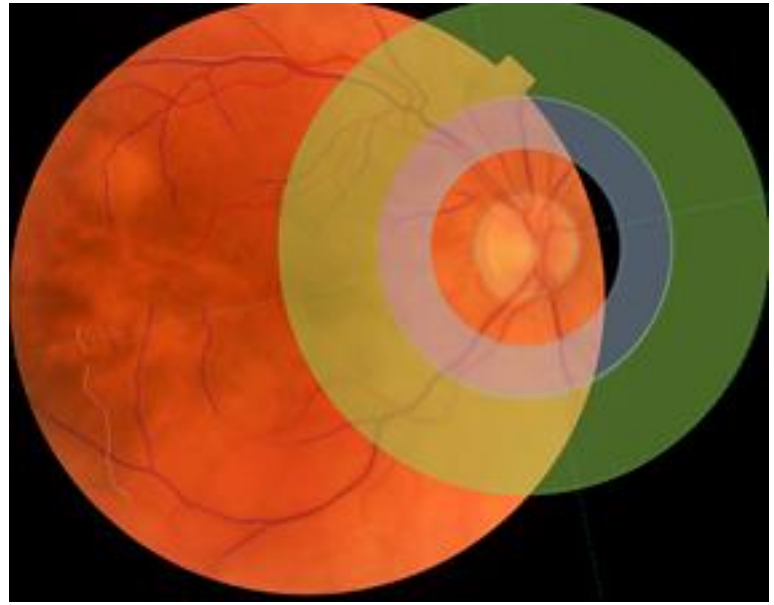
- Blood vessels within retina are called retinal vasculature
- Can be viewed using digital retinal fundus photograph.
- Fundus photograph is cost effective and non-invasive method to view health of retinal vasculature.
- Retinal vascular features (RVFs) can be derived when fundus photographs are measured by vessel assessment software.

Introduction to VAMPIRE

(Vascular Assessment and Measurement Platform for Images of the Retina)

Retinal Zones:

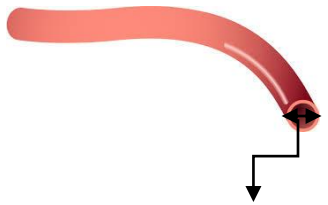
- Zone A is 0.5-1.0 optic disk diameters (ODD) from the OD centre
- Zone B is 1.0-1.5 ODD's
- Zone C is 1.0-2.5 ODD's
- VAMPIRE provides values in pixels



Zone B (used to calculate CRAE and CRVE)

Zone C (used to calculate Tortuosity and FD)

CRAE/CRVE



Diameter of Blood Vessels

Tortuosity

Bending of Blood Vessels

Fractal Dimensions

Complexity of Blood Vessels

Work Shared by E. Trucco and Team

Experiment

1. Ethnicity and Retinal Measurements

Research Question: Does ethnicity effect retinal vascular measurements in type 2 diabetes participants?

Hypothesis: Retinal measurements between two ethnic are not different

Methods

- Participants retinal photos were obtained during routine diabetic retinal screening.

Population	No. of Participants	Eye	
		Left	Right
MDRF (India)	1,874	568	1,306
GoDARTS (Scotland)	6,625	277	6,348

- Retinal vascular feature were dependent variable.
- RVFs considered for the analysis are vessel width, tortuosity and fractal dimension
- Model: RVFs ~ Ethnicity + Age + Gender + BMI + SBP + HbA1c.

Results

Mean difference between RVFs of Scottish and Indian participants

Features	Scottish Mean (μ_1), SE	Indian Mean (μ_2), SE	P-value
Arteriolar Width, pixels	32.49 (0.03)	28.81 (0.06)	<0.001***
Venular Width, pixels	42.92 (0.04)	39.38 (0.10)	<0.001***
Arteriolar tortuosity ^	-9.78 (0.01)	-10.04 (0.02)	<0.001***
Venular tortuosity ^	-9.71 (0.009)	-9.97 (0.02)	<0.001***
Arteriolar Fractal	1.51(0.0008)	1.62 (0.001)	<0.001***
Venular Fractal	1.50 (0.008)	1.60 (0.001)	<0.001***

^: Log Transformed
*p≤0.1, **p≤0.05, ***p≤0.001

Mean difference between RVFs of two population are different.

Results

Relationship between ethnicity and RVFs

Features	ß (95% CI) Base Model	P-value	ß (95% CI) Full Model	P-value
Arteriolar Width, pixels	4.62 (4.46 – 4.78)	<0.001***	4.87 (4.68 – 5.0)	<0.001***
Venular Width, pixels	3.99 (3.77 – 4.21)	<0.001***	4.22 (3.96 – 4.47)	<0.001***
Arteriolar tortuosity ^	0.32 (0.26 – 0.38)	<0.001***	0.29 (0.22 – 0.36)	<0.001***
Venular tortuosity ^	0.26 (0.22 – 0.31)	<0.001***	0.21 (0.16 – 0.26)	<0.001***
Arteriolar Fractal	-0.10 (-0.11 - -0.10)	<0.001***	-0.10 (-0.10 - -0.09)	<0.001***
Venular Fractal	-0.10 (-0.10 - - 0.09)	<0.001***	-0.09 (-0.09 - - 0.08)	<0.001***

Base Model: Age and Gender Adjusted
Full Model: Base Model + BMI + SBP + HbA1c adjusted
Reference Group: Indians

Results : Adjusting for height

Table 3: Relationship between ethnicity and RVFs

Features	ß (95% CI) Base Model	P-value	ß (95% CI) Full Model	P-value
Arteriolar Width, pixels	4.62 (4.46 – 4.78)	<0.001***	**4.83 (4.65 – 5.01)**	**<0.009**
Venular Width, pixels	3.99 (3.77 – 4.21)	<0.001***	**4.22 (3.97 – 4.46)**	**2.0×10^{-230}**
Arteriolar tortuosity ^	0.32 (0.26 – 0.38)	<0.001***	**0.31 (0.24 – 0.38)**	**8.7×10^{-20}**
Venular tortuosity ^	0.26 (0.22 – 0.31)	<0.001***	**0.25 (0.20 – 0.30)**	**3.9×10^{-21}**
Arteriolar Fractal	-0.10 (-0.11 - -0.10)	<0.001***	**-0.10 (-0.11 - -0.10)**	**<0.009**
Venular Fractal	-0.10 (-0.10 - - 0.09)	<0.001***	**-0.09 (-0.09 - -0.08)**	**4.0×10^{-297}**

Base Model: Age and Gender Adjusted
Full Model: Base Model + height + SBP + HbA1c adjusted
Highlighted rows qualify for Bonferroni Correction ($p \leq 9 \times 10^{-3}$) in the Full Model
Reference Group: Indians

Results : Adjusted for image resolution

Table 4: Relationship between ethnicity and RVFs

Features	ß (95% CI) Base Model	P-value	ß (95% CI) Full Model	P-value
Arteriolar Width, pixels	4.62 (4.46 – 4.78)	<0.001***	**0.97 (0.64 – 1.30)**	**6.9×10^{-9}**
Venular Width, pixels	3.99 (3.77 – 4.21)	<0.001***	**- 0.92 (-1.36 - -0.47)**	**5.1×10^{-5}**
Arteriolar tortuosity ^	0.32 (0.26 – 0.38)	<0.001***	**0.52 (0.39 – 0.65)**	**9.3×10^{-16}**
Venular tortuosity ^	0.26 (0.22 – 0.31)	<0.001***	**0.33 (0.23 – 0.42)**	**5.8×10^{-11}**
Arteriolar Fractal	-0.10 (-0.11 - -0.10)	<0.001***	**-0.15 (-0.16 - -0.14)**	**2.0×10^{-182}**
Venular Fractal	-0.09 (-0.10 - - 0.09)	<0.001***	**- 0.13 (-0.14 - -0.12)**	**2.0×10^{-134}**

*p≤0.1; **p≤0.05; ***p≤0.001

Base Model: Age and Gender Adjusted
Full Model: Base Model + height + SBP + HbA1c adjusted + image resolution (megapixels)
Highlighted rows qualify for Bonferroni Correction ($p \leq 9 \times 10^{-3}$) in the Full Model
Reference Group: Indians

Explanation

- Difference in measuring protocol: Macula centre and optic disc centre images
- Iris pigmentation in the participants at two study sites. Need retinal photographs from two site to compare.

Experiment

2. Relationship between clinical risk factors and retinal vascular features.

Research Question: Can clinical risk factors influence baseline retinal vascular features?

Hypothesis: Clinical risk factors influence baseline retinal vascular features

Methods

- Number of participants:

Indian: 1,870 Scotland: 6,639

- The median of each clinical measure for a 3-year period prior to the date of the fundus photograph was obtained.
- Clinical risk Factors: SBP, DBP, BMI, HbA1c, HDL, Total Cholesterol, Trig, Smoking.
- Model: RVF ~ CRF + Age + Gender

Results

	Arteriolar Calibre ß (95% CI)				Venular Calibre ß (95% CI)			
	MDRF (N=1,870)		GoDARTS (N=6,639)		MDRF (N=1,870)		GoDARTS (n=6,639)	
	Base Model	Full Model	Base Model	Full Model	Base Model	Full Model	Base Model	Full Model
SBP (per 10 mmHg)	-0.03 * (-0.08 – 0.0006)	-0.01 (-0.05 – 0.02)	-0.05 *** (-0.07 - -0.03)	-0.05 *** (-0.07 - -0.03)	0.01 (-0.02 – 0.06)	0.04 ** (0.005 – 0.08)	-0.01* (-0.03 – 0.0009)	-0.01 (-0.03 – 0.006)
DBP (per 10 mmHg)	0.008 (-0.07 – 0.09)	-0.006 (-0.09 – 0.07)	-0.04 *** (-0.07 - -0.01)	-0.05 *** (-0.08 - -0.01)	0.03 (-0.04 – 0.12)	0.01 (-0.06 – 0.10)	0.07 *** (0.04 – 0.10)	0.03 ** (0.002 – 0.07)
BMI	-0.006 (-0.01 – 0.004)	-0.007 (-0.01 – 0.003)	0.0003 (-0.003 – 0.004)	-0.004 ** (-0.008 – 0.0005)	-0.003 (-0.01 – 0.007)	-0.001 (-0.01 – 0.009)	0.007 *** (0.003 – 0.01)	0.002 (-0.001 – 0.006)
HbA1c	0.01 (-0.01 – 0.04)	0.01 (-0.02 – 0.04)	0.005 (-0.01 - 0.02)	-0.005 (-0.02 – 0.01)	0.05 (0.01 – 0.08)	0.04 (0.01 – 0.07)	0.05 *** (0.03 – 0.07)	0.04 *** (0.01 – 0.06)
HDL	-0.001 (-0.007 – 0.003)	0.001 (-0.003 – 0.007)	0.10 *** (0.04 – 0.17)	0.04 (-0.02 - 0.11)	-0.001 (-0.007 – 0.004)	0.003 (-0.002 – 0..009)	0.007 (-0.06 – 0.07)	0.01 (-0.05 – 0.08)
Non-HDL	0.07 *** 0.03 – 0.11)	0.05 ** (0.01 – 0.10)	0.003 (-0.02 – 0.03)	-0.01 (-0.04 – 0.01)	0.11 *** (0.07 – 0.15)	0.10 *** (0.06 – 0.16)	0.05 *** (0.02 – 0.08)	0.03 ** (0.003 – 0.06)
Total Cholesterol	0.06 (0.01 - 0.10)	0.05 (0.01 – 0.09)	0.02 * (-0.004 – 0.05)	-0.01 (-0.03 – 0.10)	0.09 *** (0.05 – 0.13)	0.01 *** (0.05 – 0.14)	0..06 *** (0.04 – 0.09)	0.04 *** (0.01 – 0.07)
Triglycerides	0.0002 (-0.0003 – 0.0007)	-0.0001 (0.0007 – 0.0004)	0.001 (-0.01 – 0.01)	0.0008 (-0.01 – 0.01)	0.001 ** (0.0004 – 0.001)	0.0007 ** (0.0001 – 0.001)	0.01 * (-0.0009 – 0.03)	0.0008 (-0.0008 – 0.02)
Smoking	0.06 (-0.04. -0.18)	0.02 (-0.09 – 0.14)	0.06 *** (0.01 – 0.11)	0.07 *** (0.03 – 0.12)	0.17 ** (0.05 – 0.30)	0.11 * (-0.009 – 0.23)	0.08 *** (0.03 – 013)	0.09 *** (0.04 – 0.14)

*p≤0.1; **p≤0.05; ***p≤0.001; Base Model: RVF ~ CRF; Full Model: Base Model + Age + Gender

	Arteriolar Tortuosity ß (95% CI)				Venular Tortuosity ß (95% CI)			
	MDRF (N=1,870)		GoDARTS (N=6,639)		MDRF (N=1,870)		GoDARTS (N=6,639)	
	Base Model	Full Model	Base Model	Full Model	Base Model	Full Model	Base Model	Full Model
SBP (per 10 mmHg)	0.03 (-0.01 – 0.08)	0.04 * (-0.0009 – 0.10)	0.002 (-0.01 – 0.02)	0.007 (-0.01 – 0.02)	0.01 (-0.02 – 0.05)	0.01 (-0.02 – 0.04)	0.05 *** (0.02 – 0.06)	0.04 *** (0.03 – 0.06)
DBP (per 10 mmHg)	-0.02 (-0.13 – 0.07)	-0.03 (-0.13 – 0.06)	0.01 (-0.01 – 0.04)	-0.01 (-0.05 – 0.01)	0.02 (-0.05 – 0.10)	0.03 (-0.04 – 0.10)	-0.03 ** (-0.05 – - 0.007)	-0.03 ** (-0.06 – 0.008)
BMI	0.005 (-0.007 – 0.01)	0.006 (-0.008 – 0.01)	0.007 *** (0.003 – 0.01)	0.004 ** (0.00008 – 0.009)	0.005 (-0.003 – 0.01)	0.006 (-0.003 – 0.01)	0.005 *** (0.002 – 0.008)	0.005 *** (0.002 – 0.009)
HbA1c	0.06 ** (0.02 – 0.10)	0.06 ** (0.02 – 0.10)	0.02 ** (0.004 – 0.04)	0.01 (-0.009 – 0.03)	0.02 (-0.004 – 0.05)	0.02 * (-0.004 – 0.05)	0.005 (-0.01 – 0.02)	0.006 (-0.01 – 0.02)
HDL	-0.005 (-0.01 – 0.001)	-0.004 (-0.01 – 0.002)	-0.02 (-0.09 – 0.04)	0.009 (-0.06 – 0.08)	0.004 (-0.0006 – 0.009)	0.003 (-0.001 – 0.008)	-0.01 (-0.06 – 0.04)	-0.02 (-0.08 – 0.03)
Non-HDL	0.06 ** (0.01 – 0.11)	0.06 ** (0.008 – 0.11)	0.02 (-0.005 – 0.05)	0.006 (-0.02 – 0.03)	0.02 (-0.009 – 0.06)	0.03 (-0.007 – 0.07)	-0.0002 (-0.02 – 0.02)	-0.0004 (-0.02 – 0.02)
Total Cholesterol	0.04 * (-0.0005 – 0.09)	0.04 * (-0.002 – 0.09)	0.01 (-0.01 – 0.03)	-0.002 (-0.03 – 0.02)	0.03 (-0.004 – 0.06)	0.03 (-0.004 – 0.07)	-0.001 (-0.02 – 0.02)	-0.004 (-0.02 – 0.01)
Triglycerides	0.009 ** (0.0002 – 0.001)	0.0009 ** (0.0002 – 0.002)	0.001 (-0.01 – 0.01)	-0.002 (-0.01 – 0.01)	0.0002 (-0.0002 – 0.0007)	0.0003 (-0.0002 – 0.0008)	-0.0006 (- 0.01- 0.01)	0.001 (-0.01 – 0.01)
Smoking	0.04 (-0.09 – 0.18)	0.03 (-0.11 – 0.18)	0.03 (-0.01 – 0.07)	0.02 (-0.01 – 0.07)	-0.03 (-0.13 – 0.07)	-0.02 (-0.13 – 0.08)	0.02 (-0.007 – 0.06)	0.03 (-0.005 – 0.06)

*p≤0.1; **p≤0.05; ***p≤0.001; Base Model: RVF ~ CRF; Full Model: Base Model + Age + Gender

	Arteriolar Fractal ß (95% CI)				Venular Fractal ß (95% CI)			
	MDRF (N=1,870)		GoDARTS (N=6,639)		MDRF (N=1,870)		GoDARTS (N=6,639)	
	Base Model	Full Model	Base Model	Full Model	Base Model	Full Model	Base Model	Full Model
SBP (per 10 mmHg)	-0.01 (-0.05 – 0.02)	0.007 (-0.03 – 0.04)	-0.02 * (-0.04 – 0.0009)	-0.01 (-0.03 – 0.005)	-0.06 ** (-0.10 - -0.02)	-0.04 ** (-0.08 – -0.0006)	0.02 * (-0.0009 – 0.04)	0.02 ** (0.004 – 0.04)
DBP (per 10 mmHg)	0.01 (-0.06 – 0.10)	0.004 (-0.08 – 0.09)	0.02 (-0.006 – 0.05)	-0.01 (-0.04 – 0.02)	-0.01 (-0.10 – 0.06)	-0.02 (-0.11- 0.05)	0.08 *** (0..04 – 0.11)	0.05 *** (0.01- 0.08)
BMI	-0.0003 (-0.01 – 0.01)	-0.00005 (-0.01 – 0.02)	-0.002 (-0.006 – 0.001)	-0.006 (-0.01 – - 0.002)	-0.0003 (-0.01 – 0.01)	-0.005 (-0.01 – 0.006)	0.003 (-0.001 – 0.007)	-0.0006 (-0.004 – 0.003)
HbA1c	0.02 (-0.01 – 0.04)	0.01 (-0.02 – 0.05)	-0.01 (-0.03 – 0.009)	-0.02 ** (-0.05 – -0.006)	-0.01 (-0.04 – 0.02)	-0.01 (-0.05 – 0.01)	0.01 (-0.01 – 0.03)	-0.004 (-0.02 – 0.01)
HDL	-0.004 * (-0.01 – 0.0007)	-0.002 (-0.007 – 0.003)	0.03 (-0.03 – 0.10)	0.06 * (-0.003 – 0.14)	0.001 (-0.004 – 0.006)	0.003 (-0.002 – 0.009)	0.07 ** (0.002 – 0.14)	0.11 *** (0.04 – 0.19)
Non-HDL	0.05 ** (0.01 - 0.09	0.04 * (-0.0001 – 0.08)	0.03 ** (0.007 – 0.06)	0.02 (-0.01 – 0.05)	0.05 ** (0.0088 - 0.09)	0.02 (-0.01 - 0.07)	0.04 *** (0.01 – 0.07)	0.02 (-0.005 – 0.05)
Total Cholesterol	0.03 * (-0.0007 – 0.08)	0.03 * (-0.006 – 0.07)	0.03 ** (0.002 – 0.05)	0.01 (-0.01- 0.04)	0.04 ** (0.005 – 008)	0.02 (-0..01 – 0.07)	0.05 *** (0.02 – 0.08)	0.03 *** (0.01 – 0.06)
Triglycerides	0.0005 * (-0.00004 – 0.001)	0.003 (-0.002 – 0.0009)	-0.0009 (-0.01- 0.01)	-0.005 (-0.02 – 0.01)	0.0005 (-0.00003 – 0.001)	0.0002 (-0.0003 – 0.0008)	-0.002 (-0.01 – 0.01)	-0.006 (-0.02 – 0..01)
Smoking	0.10 * (-0.01 – 0.21)	0.06 (-0.05 – 0.19)	-0.01 (-0.06 – 0.03)	-0.01 (-0.06 – 0.03)	0.03 (-0.07 – 0.15)	0.04 (-0.07 – 0.17)	0.008 (-0.04 – 0.05)	0.007 (-0.04 – 0.05)

*p≤0.1; **p≤0.05; ***p≤0.001; Base Model: RVF ~ CRF; Full Model: Base Model + Age + Gender

Conclusion

- Non-HDL cholesterol and smoking widen venular calibre among Indian participants and Scottish participants.
- BMI increases arteriolar and venular tortuosity among Scottish participants compared to Indian participants.
- DBP, Total Cholesterol and HDL increases venular fractals among Scottish participants compared to Indian participants.

Experiment

3. Relationship between retinal vascular features and microvascular complications among Indians

Methods

- Microvascular Complications of interest are diabetic retinopathy, chronic kidney disease and diabetic peripheral neuropathy
- Definition of complications:

Cases: Ever microvascular complications before the retinal photo

Control: Never microvascular complications + one year after photo

- Cross-sectional Study Design (Logistic Regression)

Results: Relationship between any DR and RVFs

Total Participants: 1,768
Cases: 870 (49.21%)
Control: 898

Features	OR (95% CI) Base Model	P-value	OR (95% CI) Full Model	P-value
Arteriolar Width$	1.00 (0.97 – 1.03)	0.84	0.97 (0.94 – 1.01)	0.19
Venular Width$	1.02 (1.00 – 1.04)	0.02**	1.00 (0.98 – 1.03)	0.47
Arteriolar tortuosity ^	1.11 (1.02 – 1.20)	0.008***	1.05 (0.97 – 1.15)	0.20
Venular tortuosity ^	1.06 (0.95 – 1.18)	0.26	1.04 (0.92 – 1.17)	0.46
Arteriolar Fractal$	0.93 (0.85 – 1.03)	0.17	0.88 (0.79 – 0.98)	0.02**
Venular Fractal$	0.92 (0.83 – 1.01)	0.10	0.95 (0.85 – 1.06)	0.42

$: standardize; ^ Log Transformation *p≤0.1; **p≤0.05; ***p≤0.01
Base Model: Age and Gender Adjusted
Full Model: Base Model + HbA1c + Duration of T2D

Results: Relationship between PDR and RVFs

Total Participants: 1,768
Cases: 56 (3.17%)
Control: 1,712

Features	OR (95% CI) Base Model	P-value	OR (95% CI) Full Model	P-value
Arteriolar Width$	0.92 (0.83 – 1.01)	0.09*	0.91 (0.83 – 1.02)	0.13
Venular Width$	1.01 (0.96 – 1.08)	0.52	1.01 (0.95 – 1..07)	0.60
Arteriolar tortuosity ^	1.02 (0.82 – 1.28)	0.80	0.99 (0.78 – 1.24)	0.93
Venular tortuosity ^	0.95 (0.70 – 1.28)	0.77	0.90 (0.66 – 1.23)	0.53
Arteriolar Fractal$	0.72 (0.57 – 0.92)	0.009***	0.71 (0.55 – 0.91)	0.008***
Venular Fractal$	0.73 (0.59- 0.89)	0.003***	0.76 (0.62 – 0.94)	0.011**

$: standardize; ^ Log Transformation *p≤0.1; **p≤0.05; ***p≤0.01
Base Model: Age and Gender Adjusted
Full Model: Base Model + HbA1c adjusted + Duration of T2D

Results: Relationship between CKD-Stage 3 and RVFs

Total Participants: 1,874
Cases: 190 (10.13%)
Control: 1,684

Features	OR (95% CI) Base Model	P-value	OR (95% CI) Full Model	P-value
Arteriolar Width$	0.93 (0.88 – 0.98)	0.012**	0.92 (0.87 – 0..97)	0.007**
Venular Width$	0.99 (0.95 – 1.02)	0.64	0.98 (0.95 – 1.02)	0.53
Arteriolar tortuosity ^	0.93 (0.82 – 1.05)	0.26	0.94 (0.82 – 1.07)	0.39
Venular tortuosity ^	0.94 (0.79 – 1.12)	0.54	0.87 (0.72 – 1.05)	0.16
Arteriolar Fractal$	0.97 (0.83 – 1.13)	0.72	0.99 (0.84 – 1.16)	0.91
Venular Fractal$	0.85 (0.74 – 0.98)	0.03**	0.88 (0.76 – 1.03)	0.12

Definition of CKD – Stage 3 eGFR≤60 ml/min/1.73m^2 (CKD-EPI equation)

$: standardize; ^ Log Transformation *p≤0.1; **p≤0.05; ***p≤0.001
Base Model: Age and Gender Adjusted
Full Model: Base Model + HbA1c + Duration of T2D + SBP + HDL + BMI + Smoking

Results: Relationship between DPN and RVFs

Total Participants: 1,768
Cases: 1,149 (64.98%)
Control: 619

Features	OR (95% CI) Base Model	P-value	OR (95% CI) Full Model	P-value
Arteriolar Width$	1.06 (0.96 – 1.04)	0.71	1.00 (0.96 – 1.04)	0.89
Venular Width$	1.02 (0.99 – 1.04)	0.08	1.01 (0.99 – 1.04)	0.18
Arteriolar tortuosity ^	1.11. (1.01 - 1.21)	0.01**	1.09 (1.00 – 1.20)	0.04**
Venular tortuosity ^	1.07 (0.94 – 1.21)	0.27	1.06 (0.93 – 1.20)	0.33
Arteriolar Fractal$	1.07 (0.96 – 1.20)	0.21	1.06 (0.95 – 1.19)	0.26
Venular Fractal$	0.96 (0.85 – 1.08)	0.51	0.97 (0.86 – 1.10)	0.71

$: standardize; ^ Log Transformation *p≤0.1; **p≤0.05; ***p≤0.001
Base Model: Age and Gender Adjusted
Full Model: Base Model + HbA1c + Duration of T2D

Conclusion

- Risk of DR increases when arteriolar fractals decreases.
- Risk of CKD stage 3 increases with narrower arteriolar width.
- Risk of DPN is increased with increased in tortuosity.

Funded by

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Thank You

- Alex Doney
- Emanuele Trucco
- Guha Pradeepa
- Yvonne
- Health Informatics Centre
- Stephen Hogg
- Gittu George
- Abi Velluchamy
- INSPIRED Team Members
- MDRF Team Members