RELATIONSHIP BETWEEN CLINICAL RISK FACTORS AND RETINAL VASCULAR MEASUREMENTS AMONG TYPE 2 DIABETES PATIENTS: A GODARTS STUDY

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Introduction and Project Aim

- Cardiometabolic clinical risk factors (CRFs) effect on the vascular systems in human body and thereby result in complications on type 2 diabetes (T2D). (1)
- Type 2 diabetic (T2D) patients have increased risk of cardiovascular diseases (CVD) due to complex combination of CRFs. (1)
- Previous studies have attempt to establish the additional plasma bio-markers but these provided limited evidence. (2)
- The retinal vasculature can provide vital information on vascular health which can be used as a imaging bio-marker for early detection of the CVD. (2)

➢ This study **aims** to understand the relationship between CRFs and change in retinal microvasculature measured both at baseline and between two time points (3 years).

Hypothesis: Baseline CRFs can affect a. baseline retinal measurements and b. temporal change in retinal measurements.

Methods

- T2D participants were drawn from Genetic of Diabetes Audit and Research in Tayside Scotland (GoDARTS).
- Retinal images were measured using VAMPIRE software (Version 3.1) developed by University of Dundee. Retinal measurements for right eye were *included* for the analysis.
- Retinal measure like vessel width, fractal dimensions and tortuosity of arterioles and venules respectively, were the retinal features included for the analysis.
- The median of each CRF measure for a 3-year period prior to the date of the first (baseline) fundus image was obtained. (Fig. 1).

Clinical Risk Factors (CRFs) Considered

- ❖ Systolic and Diastolic Blood Pressure (SBP/DBP).
- ❖ Body Mass Index (BMI).
- ❖ Glycated Hemoglobin (HbA1c).
- ❖ Lipids (HDL, Triglycerides & Total Cholesterol).
- ❖ Smoking.

Experiment 1: Effect of CRFs on baseline retinal measurements (RM)

1. A total of 6,645 participants had retinal measurements at baseline.
2. 5,787 (87.08%) participants had complete information on retinal measurement and CRFs (included for analysis).

Statistical Analysis

Linear Regression

Model 1: RM (baseline) ~ CRF (median) + age + gender

Results are interpreted using Bonferroni Correction

Experiment 2: Effect of CRFs on temporal change RM (ΔRM)

1. 1,773 participants had complete information on retinal measurements and CRFs of interest and also second retinal image.
2. 251 participants had time difference (ΔT)between two retinal screening ≤1 year and ≥5 years respectively, excluded from the analysis.

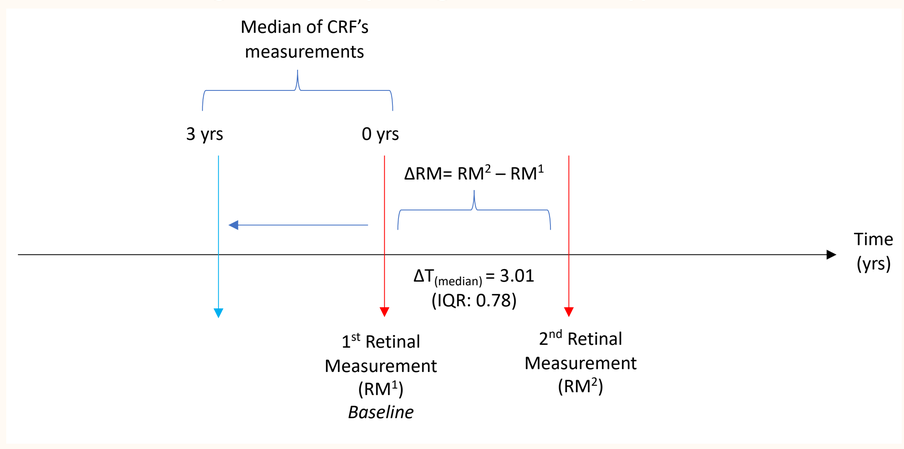
Statistical Analysis

Linear Regression

Model 2: $\Delta RM \sim CRF_{(median)} + age + gender + RM_{(baseline)} + \Delta T$.

Results are interpreted using Bonferroni Correction

Figure 1: Study design to test the hypothesis



Results

Table 1: Characteristics of participants included in Experiment 1 and Experiment 2

Variables	At Baseline	ΔRM
Number of participants	5,787	1,330
Median Age (IQR), yrs	67 (15.35)	66.25 (13.02)
Female (%)	55.43	51.65
Ever smokers (%)	50.06	48.12
Median SBP (IQR), per 10 mm of Hg	13.9 (1.3)	13.9 (1.3)
Median DBP (IQR), per 10 mm of Hg	7.6 (1.1)	7.6 (1.1)
Median BMI (IQR), kg/m²	30.30 (7.4)	30.6 (7.89)
Median HbA1c (IQR), %	7.3 (1.4)	7.25 (1.38)
Median HDL (IQR), mmol/L	1.28 (0.4)	1.29 (0.41)
Median Total Cholesterol (IQR)	4.3 (1)	4.34 (1.01)
Median Triglycerides (IQR), mmol/L	1.86 (1.44)	1.89 (1.38)

Table 2: Association between clinical risk factors and retinal measurement at baseline (N=5,787) [Experiment 1]

Univariate regression models adjusted for age and gender

Clinical Risk Factors (CRFs)	Vessel Width (A) $	Vessel Width (V) $	Tortuosity (V) #	D_f (V)
	ß (95% CI)	ß (95% CI)	ß (95% CI)	ß (95% CI)
SBP (Per 10 mm of Hg) n = 5,296	**- 0.05 *** $$ (-0.07 - -0.03)**	- 0.009 (-0.03 – 0.01)	**0.05 *** $$ (0.03 – 0.08)**	0.002 (0.007 – 0.003)
DBP (Per 10 mm of Hg) n = 5,296	- 0.03 (-0.07 – 0.001)	0.05 ** (0.02 – 0.09)	- 0.03 (- 0.06 – 0.01)	**0.004 ** $$ (0.001 – 0.007)**
HbA1c n = 5,511	- 0.008 (- 0.03 – 0.01)	**0.05 *** $$ (0.02 – 0.07)**	0.01 (- 0.009 – 0.03)	- 0.00004 (- 0.001 – 0.001)
HDL n = 5,162	- 0.01 (- 0.08 – 0.05)	- 0.01 (- 0.08 – 0.05)	- 0.06 (- 0.14 – 0.01)	**0.008 *** $$ (0.003 – 0.01)**

Retinal width measurements are in pixels ; # Log Transformed. $: z-transformed ; *p≤0.05, **P≤0.001, ***p≤0.0001

$$ Bonferroni Correction: Calculated using n=a/k; a=0.05; k=8*6=48; 0.05/48=0.0001; hence new threshold of p≤0.0001 is applied (in bold).

➢ *Arteriole tortuosity and fractal dimension, BMI, Total Cholesterol, Triglycerides and Smoking were checked for association, but did not show any significant results according to Bonferroni criteria, hence results not shown.*

Table 3: Multivariate (stepwise backward regression) analysis between clinical risk factors and change in retinal measurements at two time points (n = 553) [Experiment 2]

Regression models adjusted for age, gender, retinal measurements at baseline, platform and time difference between two retinal measurements

Clinical Risk Factors (CRFs)	Vessel Width (A) $	Vessel Width (V) $
	ß (95% CI)	ß (95% CI)
SBP (Per 10 mm of Hg)	-	- 0.07 * (- 0.13 – 0.0001)
DBP (Per 10 mm of Hg)	0.11 ** (0.02 – 0.19)	0.13 ** (0.02 – 0.22)
HbA1c	- 0.07 ** (- 0.13 - -0.01)	-

Retinal width measurements are in pixels; $: z-transformed ; *p<0.1, **p<0.05, ***p<0.0001

Venular tortuosity and fractal dimension were checked for association in this model, but did not show any significant results, hence data not shown.

➢ *Variable which showed significant association in multivariate analysis were only reported.*

Conclusion

Experiment 1 shows that as SBP increases, venular tortuosity also increases, but arteriolar vessel width are decreased. Also, increase in DBP and HDL show significantly increase in venular fractal dimension. Increase in HbA1c significantly increases venular vessel width.

Experiment 2 shows that DBP significantly increases arteriolar and venular vessel width. But HbA1c and SBP significantly decreases arteriolar and venular vessel width respectively. These experiments shows that retinal measurements can be used as a potential imaging bio-marker for vascular health.

However, further investigation is required using longitudinal retinal measurements to understand the effect of CRFs on retinal vasculature over time.

Reference:
1. Iciar Martín-Timón, Cristina Sevillano-Collantes, Amparo Segura-Galindo, et al. Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength?; World J Diabetes. 2014 Aug 15; 5(4): 444–470.
2. Owen CG, Rudnicka AR, Welikala RA, et al. Retinal Vasculometry Associations with Cardiometabolic Risk Factors in the European Prospective Investigation of Cancer-Norfolk Study. Ophthalmology. 2019;126(1):96-106. doi:10.1016/j.ophtha.2018.07.022

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