AN EXPLORATORY STUDY OF OPTIC NERVE HEAD VASCULAR FRACTAL DIMENSION (Df) AND ITS ASSOCIATION WITH DIABETES MELLITUS RISK FACTORS

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INTRODUCTION

The prevalence of diabetes mellitus (DM) is increasing, and there are many patients with undiagnosed DM. Fundus screening of individuals with risk of developing DM may help its diagnosis. Smartphone-assisted fundus photography (SAFP) may serve as a screening tool to detect early retinal changes in DM. SAFP such as the Portable Eye Examination Kit (Peek Retina™; Peek Vision Ltd, England, UK) provides an opportunity to study retinal vascularity using the fractal dimension (Df) analysis. Digital retinal images using SAFP has been shown to provide a reliable evaluation of retinal vascular complexity using Df analysis (Esa et al., 2019). Previous studies have shown that retinal vascular Df is associated with systemic diseases including diabetes mellitus (Aliahmad et al., 2014), hypertension (Zhu et al., 2014) and chronic kidney disease (Sng et al., 2010). In this exploratory study, the retinal optic nerve head (ONH) vascular Df was compared between populations with and without risk factors of DM.

OBJECTIVES OF THIS STUDY :

1. To compare ONH retinal vascular Df between healthy population with risk, and without risk of DM.
2. To explore the potential association of Df value to DM risk factors.

METHODOLOGY

Ninety participants comprised of 45 individuals with and without risk of DM were recruited.

Inclusion criteria:
- Malay ancestry
- Age within 18 to 50 years
- Refractive error of spherical equivalence ranged between Plano to -4.00DS

Exclusion criteria:
- Systemic diseases (except hypertension)
- Ocular diseases
- Media opacities
- Trauma history to the eye

The Diabetes Risk Test Questionnaires (American Diabetes Association, 2018) was adopted to classify participants into the groups.

1. How old are you?
   Less than 40 years (0 points)
   40—49 years (1 point)
   50—59 years (2 points)
   60 years or older (3 points)
2. Are you a man or a woman?
   Man (1 point) Woman (0 points)
3. If you are a woman, have you ever been diagnosed with gestational diabetes?
   Yes (1 point) No (0 points)
4. Do you have a mother, father, sister, or brother with diabetes?
   Yes (1 point) No (0 points)
5. Have you ever been diagnosed with high blood pressure?
   Yes (1 point) No (0 points)
6. Are you physically active?
   Yes (0 points) No (1 point)
7. What is your weight status?

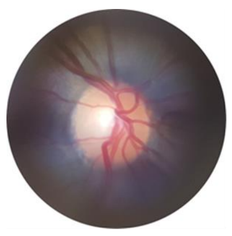
Anthropometric measurements were measured.

1. Blood pressure measurement *(Blood Pressure Monitor; HEM-907, OMRON, Japan)*
2. Physical activity evaluation *(International Physical Activity Questionnaire – Short; IPAQ-S)*
3. Dietary intake assessment *Nutritionist Pro™ Version 4.0.0 (Axxya System, USA)*
4. Body weight and height measurement

Retinal images were taken using Peek Retina™ attached to a smartphone.

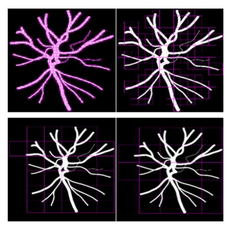
Suitable images which met criteria; 1) Good focus, 2) Centered position on optic nerve head (ONH) and 3) Significant blood vessel visibility were selected.

All images were cropped 0.5-disc diameter away from the disc margin and resized to 500x500 pixels using GIMP.



Retinal images were segmentally traced using SketchBook Pro for Galaxy Apps.

Traced images were analyzed using Image J and FracLac software by box counting method to obtain Df value.



Statistical analysis were performed using SPSS software version 21.

- Independent t-test was employed to compare ONH vascular Df between groups with and without DM risk factors.

- Analysis of covariance (ANCOVA) was used to explore the association between retinal Df values and DM risk factors.

RESULTS

Table 1: Comparison of retinal Df between groups with non-risk and with risk of DM (n=90)

	ONH Df Non-risk group Mean ± SD (n=45)	ONH Df Risk group Mean ± SD (n=45)	p-value
No adjusted variable	1.475 ± 0.020	1.476 ± 0.032	0.818 (Independent t-test)
Adjusted for age, sex, marital status, BMI, SBP, DBP, MAP, DRTQ Score, GDM, history of DM and hypertension	1.469 ± 0.012	1.482 ± 0.013	0.242 (ANCOVA)

Table 2: Relationship of DM risk factors with retinal vascular Df

	Number (n)	Mean Df[a]	SE	p-value (ANCOVA)
Age (years)				0.815
1st quartile (≤ 24)	32	1.474	0.007	
2nd quartile (25 – 28)	15	1.481	0.008	
3rd quartile (29 – 39)	21	1.477	0.007	
4th quartile (≥ 40)	22	1.472	0.008	
Sex				0.483
Male	42	1.472	0.005	
Female	48	1.478	0.005	
GDM				0.467
Yes	6	1.484	0.012	
No	84	1.475	0.003	
History of DM				0.547
Yes	44	1.473	0.005	
No	46	1.477	0.005	
Hypertension				0.686
Yes	35	1.478	0.008	
No	55	1.473	0.006	
Physically Active				0.788
Yes	16	1.477	0.007	
No	74	1.475	0.003	
Systolic BP (mmHg)				0.558
1st quartile (≤ 112)	26	1.467	0.009	
2nd quartile (113 – 124)	21	1.475	0.007	
3rd quartile (125 – 140)	23	1.474	0.007	
4th quartile (≥ 141)	20	1.489	0.011	
Diastolic BP (mmHg)				0.882
1st quartile (≤ 73)	27	1.474	0.008	
2nd quartile (74 – 85)	23	1.480	0.006	
3rd quartile (86 – 92)	18	1.474	0.008	
4th quartile (≥ 93)	22	1.473	0.008	
Mean Arterial Pressure (mmHg)				0.096
1st quartile (≤ 85)	24	1.470	0.009	
2nd quartile (86 – 97)	21	1.483	0.007	
3rd quartile (98 – 108)	23	1.466	0.007	
4th quartile (≥ 109)	22	1.485	0.009	
IPAQ-S Score (MET-minutes/week)				0.248
1st quartile (≤ 240)	24	1.484	0.006	
2nd quartile (241 – 685)	21	1.479	0.006	
3rd quartile (686 – 1643)	23	1.471	0.006	
4th quartile (≥ 1644)	22	1.468	0.006	
BMI (kg/m²)				0.709
1st quartile (≤ 23.2)	27	1.483	0.007	
2nd quartile (23.3 – 28.6)	25	1.472	0.006	
3rd quartile (28.7 – 32.5)	34	1.473	0.006	
4th quartile (≥ 32.6)	4	1.466	0.015	

GDM, gestational diabetes mellitus; DM, diabetes mellitus; BP, blood pressure; IPAQ-S, international physical activity questionnaires; BMI, body mass index
[a] Adjusted for age, sex, marital status, BMI, SBP, DBP, MAP, DRTQ score, GDM, history of DM and hypertension

DISCUSSION

A. Comparison of ONH Df values between groups with risk and without risk of DM

Non-significant results suggest different retinal regions besides ONH may be affected.

PEEK retina used in capturing retinal images provided 20°- 30° FOV of ONH image. Microvasculature in peripheral region may yield different result as compared to vessels from ONH.

Adverse changes of blood vessels may initially be noticed in the peripheral retinal area (Velayutham et al., 2017).

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Our findings indirectly suggest that the retinal vessels in peripheral area may be more susceptible to undergo rarefaction as compared to in the central area.

In early development of DM, hyperglycemia may first cause damage to the pericytes around the endothelial cells of vessels (Ejaz et al., 2008).

This area consists of smaller retinal vasculatures which are structurally stabilized by a cluster of pericytes (Tell et al., 2006)

B. Potential association between retinal Df values and DM risk factors

01
Associations between DM risk factors including age, hypertension and obesity, on retinal vascular network complexity have been assessed previously (Wiharto et al., 2018).

02
Age was shown to have strong inverse correlation with retinal vascular networks where older population has lower retinal Df (Che Azemin et al., 2012).

03
A study has demonstrated that retina of patients with hypertension had lower retinal Df values compared to healthy retina (Liew, et al., 2008).

04
A study reported that increased BMI values (≥ 30kg/m²) was significantly associated with higher retinal vascular Df when compared with non-obese population (Tai et al., 2018).

05
Diabetic population significantly have lower Df values (Cheung et al., 2012).

Lower Df value was due to retinal neurodegeneration that caused significant thinning of retinal neuron layer (Ferreira et al., 2016).

06
Hyperglycemia caused apoptosis of retinal ganglion cells in the inner retina (Barber et al., 2011).

This leads to thinning of retinal nerve fiber layer (Dijk et al., 2012) which reported to be associated with reduction of retinal Df (Frydkjaer-Olsen et al., 2015).

07
In relation with current study, those with risk of DM is considered healthy non-diabetics individuals as the disease is clinically yet to develop.

This indicated no or minimal loss of retinal blood vessels as no underlying of retinal neurodegenerative process take places when comparing with diabetic.

08
Longitudinal research regarding neural degeneration and retinal Df on non-risked, risked and early diabetic population need to be investigated to determine the cut-off point of retinal Df values in relation with retinal degeneration process.

CONCLUSION

This study demonstrated that ONH vascular Df values was not influenced by DM risk factors. Assessment on ocular fundus, particularly on the ONH vasculatures, using images from SAFP yield no significance between groups which may suggest for imagery on other retinal loci.

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