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Comparison of the Foveal Avascular Zone in Diabetic Retinopathy, High Myopia and Normal Fundus Images.

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ABSTRACT

To quantitatively describe and evaluate a new image processing technique for estimating the Foveal Avascular Zone (FAZ) in subjects with Diabetic Retinopathy and myopes. From a total of 328 images obtained from Diabetic Retinopathy (113), myopes (120) and normal (93), the FAZ dimensions were quantified using a new image processing algorithm. These parameters were also determined manually and by the OCT manufacturer's inbuilt algorithm. In the new technique, the images were first pre-processed by using a DOG filter iteratively before being complemented followed by a Prewitt edge detection and repeated image dilation at angles of 0^0, 45^0 and 90^0. Image closure was then applied followed by noise and small object removal which resulted in the segmented boundary. For deeper insight into shape change, in addition to the diameter of the FAZ other parameters such as the area, diameter, major axis, minor axis, orientation, perimeter vessel avascular density (VAD), Vessel diameter Index (VDI), etc. were obtained. The circularity index was calculated using the FAZ area and perimeter parameters. The mean FAZ diameter (mm) by the new automated technique, manual-segmentation (ground truth), and inbuilt instrument algorithm were 0.67 ± 0.87, 0.67 ± 0.72 and 0.61 ± 0.14. The mean of FAZ area (mm^2) was 0.36 ± 0.10, 0.33 ± 0.09 and 0.43 ± 0.14 in normal, myopia and diabetic subjects respectively. The new technique shows considerable improvement in accuracy (mean ± SD) when compared to the inbuilt system segmentation and the ground truth (manual marking by an expert clinician). The study results show that the FAZ area in Diabetic Retinopathy is significantly different (p=0.003) when compared to myopic eyes (p=0.016) and normals.

Keywords: Automated Measurement, Foveal Avascular Zone, Myopia, Diabetic Retinopathy, Optical Coherence Tomography Angiography, Image Processing.

1. INTRODUCTION

The fovea has the maximum cone photoreceptor packing density, the rod-free zone of the central retina[1] and oxygen consumption. The capillary-free zone and superficial retinal layers are displaced from the fovea resulting in the characteristic foveal pit.[1] This central avascular zone is known as the foveal avascular zone (FAZ)[1]. The size and shape of the FAZ has been quantified by multiple methods (Table 1) including entoptically,[2,3] Fundus fluorescein angiography (FFA),[4,5] Adaptive Optics Scanning Laser Ophthalmoscopy (AOSLO), [1,6] Heidelberg Retina Angiograph,[7] Retinal Functional Imager[8,9] as well as by Optical Coherence Tomography Angiography (OCTA).[7–14] Depending on the vascular pattern, the physiological shape of the FAZ is oval or round and has an average diameter of 0.40 mm to 0.60 mm.[15] Previous studies have shown that the dimensions of the FAZ varied significantly even in healthy subjects[16] (Table 1). In particular, the FAZ diameter is highly variable in normal humans and various ocular conditions such as myopia, Diabetic Retinopathy[14,17], and many more (Table 2). Linderman et al.[18] and Magrath et al.[13] reported that the FAZ area had the largest amount of variance resulting from inter-subject differences (93.1%). Multiple studies show that the dimensional metrics of the FAZ morphology exhibit excellent repeatability and reliability.[19,20]

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The retinal microvascular circulations are affected in diabetes subjects especially in poorly or uncontrolled DM subjects and leads to blindness.[21] In diabetic eyes, the vascular network terminates in the central macula and forms a ring at the peripheral edge of the FAZ.[24] The enlargement of the FAZ observed with fundus fluorescein angiography (FFA) of the diabetic eye may indicate a poor prognostic visual outcome.[22,23] Hence the severity of diabetic maculopathy can be partly determined by the size and alteration of FAZ[24]. This alteration is manifested, for example, by the circularity or area of the FAZ.[25] Subjects with disrupted foveal development (e.g., retinopathy of prematurity) appear to have a size reduction or absent FAZ.[26,27] In myopic eyes especially in high myopia, there is a narrowing of the blood vessel diameter[28] with an unchanged ocular blood flow velocity.[29] An enlargement of the FAZ area has been reported by multiple authors.[30–33]

Table 1: FAZ area in normals as reported in the literature

Author	Method	No. of eyes	Mean Age	FAZ Area ($mm^2 \pm$ SD)
Conrath[34]	FFA	31	48.4	0.15 ± 0.10
Tam[6]	AOSLO	10	27.0	0.32 ± 0.11
Nelson[8]	RFI	37	34.8	0.13 ± 0.10
Popovic[35]	Dual-conjugate Adaptive Optics	5	40.0	0.30 ± 0.10
John[7]	FFA using HRA2	31	29.7	0.28 ± 0.01
Dubis[9]	RFI, AOSLO, FFA	42	26.5	0.42 ± 0.25
Chui[1]	AOSLO	15	20-54	0.33 ± 0.19
Kim[36]	Phase-variance OCT	2	46.0	0.18
Samara[16]	RTVue XR Avanti	70	NA	0.27 ± 0.10
Takase[37]	OCT comparing enFace imaging	19	NA	0.25 ± 0.06
Di[38]	SSADA OCTA	85	53.81	0.36 ± 0.11
Magrath[13]	RTVue XR Avanti	50	NA	0.27
Carpineto[39]	RTVue XR Avanti	60	NA	0.25 ± 0.10
Gadde[40]	SSADA OCTA	52	20-67	0.35 ± 0.01
Kuehlewein[41]	Cirrus HD-OCT	13	31.0	0.30 ± 0.13
Mammo[42]	Speckle variance OCT	25	27.6	0.26 ± 0.21
Coscas[43]	RTVue XR Avanti	135	48.3	0.28 ± 0.10
de Carlo[44]	RTVue XR Avanti	22	54.0	0.29 ± 0.14
Shahlaee[11]	RTVue XR Avanti	34	NA	0.27 ± 0.10
Iafe[45]	RTVue XR Avanti	113	48	0.29 ± 0.10
Garrity[46]	RTVue XR Avanti	152	42	0.27 ± 0.10
La Spina[47]	RTVue XR Avanti	24	27.0	0.27 ± 0.05
Falavarjani[27]	RTVue XR Avanti	70	42.8	0.32 ± 0.11
Liu[48]	RTVue XR Avanti	174	38.7	0.33 ± 0.11
Mihailovic[49]	[A] RTVue XR Avanti	24	30.6	[A] 0.31 ±0.09
	[B] OCT-HS100			[B] 0.30 ±0.09
	[C] Spectralis			[C] 0.33 ±0.09
Linderman[19]	RTVue XR Avanti	116	30.5	0.26 ± 0.10
Shiihara[50]	[A] DRI Triton	27	36.8	[A] 0.26 ± 0.07
	[B] RS 3000 advance			[B] 0.28 ± 0.07
	[C] Cirrus HD-OCT			[C] 0.26 ± 0.06
	[D] Cirrus HD-OCT			[D] 0.25 ± 0.07
Guo[51]	Cirrus HD-OCT	25	55.0	0.37 ± 0.11
Rommel[52]	OCTA (5X5)	20	30.66	0.29 ± 0.10
Corvi[53]	RTVue XR Avanti	36	28.1	0.22 ± 0.10
	AngioPlex			0.23 ± 0.10
Kulikov[54]	REVO	36	51.2	0.33 ± 0.10
Linderman[18]	Cirrus HD-OCT	350	27.9	0.28 ± 0.10
Schwartz[12]	Heidelberg Spectralis SD-OCTA	47	34.0	0.32 ± 0.10
Wylęgała[25]	Cirrus HD-OCT	43	68.23	0.28 ± 0.01
Wylęgała[25]	Cirrus HD-OCT	51	65.31	0.33 ± 0.01

Table 2: Alteration of the FAZ in pathology and with aging

Author	Conditions	Reported changes in FAZ
Tan[20]	Normal & Age related changes	The FAZ areas varied significantly among healthy eyes. The center retinal thickness, gender, spherical error, axial lenght & choroidal thickness influence the size of the FAZ.
Gołębiewska[33]	Myopia	Vessel density is decreased and FAZ area is enlarged
He [32]	Myopia	An enlarged area of FAZ in eyes with High Myopia
Milani[30]	Myopia	A reduced superficial vascular density and increased outer retina flow and a statically insignificant decreased FAZ area reported
Sung[31]	Myopia	An enlarged area of FAZ in eyes with High Myopia
Li[29]	High Myopia	The retinal microvessel density was altered in both superficial and deep vascular layers with blood flow velocity remained unchanged
Mintz-Hittner[26]	Retinopathy of Prematurity	A small or absent of FAZ
Falavarjani[27]	Children Born Preterm	A small or absent of FAZ
Tao[55]	Paediatric Diabetes Type I	A statically insignificant increase reported in FAZ area and perimeter
Thompson[56]	Diabetic without clinical Diabetic Retinopathy	A statically insignificant decreased FAZ area reported
Mehta[14]	Diabetic Retinopathy	Diabetic Retinopathy have significantly enlarged FAZ areas on OCTA compared with healthy controls
De Carlo[44], Arya[57] & Takase[37]	Diabetic Retinopathy	Remodelling & enlargement of the FAZ even before microaneurysms, which 1st clinical sign of Diabetic Retinopathy.
Durbin[58]	Diabetic Retinopathy	A statically insignificant increase FAZ area reported. The FAZ perimeter showed a statically significant increase.

Given these methodological as well as disease variability it is important to measure the FAZ dimensions accurately. It is evident from Table 1 that the quantification of FAZ is highly variable and there is no standardized method to measure these dimensional parameters. Designing an accurate method to measure foveal dimensions in normal which can be used to discriminate pathologic fovea appreciating from normal age-related changes is of greater importance. The aim of our study was to describe and evaluate a new image processing technique for estimating the FAZ in subjects with Diabetic Retinopathy as well as myopes and compare them with normal data.

2. METHODOLOGY

2.1. Subjects:

This study was approved by the Institutional Review Board (IRB) of the Vision Research Foundation, Chennai, India. The study was conducted in accordance with the tenets of the Declaration of Helsinki. Exclusion criteria included any prior history or clinical evidence of retinal or systemic vascular disease. This study was a retrospective chart review of patients who had undergone comprehensive ophthalmic examinations that included OCTA at a tertiary eye care insititue in south India between January 1, 2019 and August 31, 2019. The total number of images included in the study was 328 (188 males, 140 female). The mean ± SD age was 30.5 ± 14.5 years (age range, 8 – 77 years). In this study myopic eyes were defined into two groups based on mean spherical equivalent (MSE)[59,60], namely Low-Moderate Myopia (MSE between -0.12 to < -8.00 D), and High myopia (MSE > - 8.00). The MSE was calculated from the manifest refraction during the ophthalmic evaluation. The diabetic eyes were classified based on the severity of diabetic retinopathy.[61] A single clinical expert graded all the fundus images for diabetic retinopathy based on the standardized severity scale. The images were classified into: No Diabetic Retinopathy + Mild Non-PDR as Group 1, Moderate Non-PDR as Group 2, and Severe Non-PDR and Proliferative Diabetic Retinopathy(PDR) as Group 3.

2.2. Optical Coherence Tomography Angiography and FAZ

All the OCTA was performed using a commercially available Cirrus 5000 Angioplex (Carl Zeiss Meditec Inc., Dublin, CA). All images of the macula were centered on the foveola. The device automatically segments the area into four layers that include the superficial capillary plexus layer (SL), deep capillary plexus layer (DL), outer retinal layer, and the

choriocapillaris. Every OCTA en-face image contains 6 X 6 mm (420 x 420 pixels) created from the intersection of the 420 vertical and the 420 horizontal B-scans. The automatically segmented superficial capillary plexus layer image was used for the new image processing technique. (Figure 1).

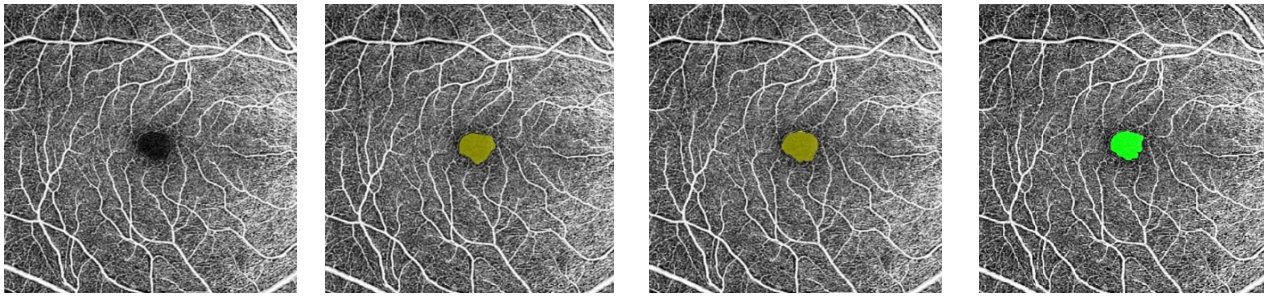


Figure 1: An example of FAZ plotting by three different methods: (A) Clear and unmarked FAZ Superficial retinal vascular plexus. (B) FAZ plotted by the manufacturer's inbuilt algorithm. (C) FAZ plotted by the manual method (ground truth). (D) FAZ plotted by the new automated image processing algorithm.

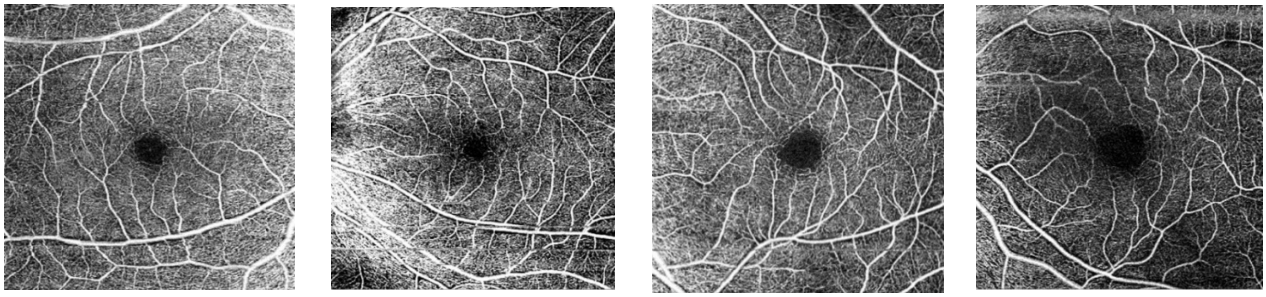


Figure 2: Sample FAZ images showing the alteration in size and shape in myopia and Diabetic Retinopathy. (A) Low-moderate myopia: almost normal size and shape (B) High myopia: reduced FAZ Area retinal vascular plexus. (C)DR: minimal size/area changes in FAZ; (D) Severe Non-PDR/PDR: enlarged and irregular FAZ area.

2.3. Assessing the Foveal Avascular Zone[62]

Three different methods were used for quantifying the FAZ dimensions in normal, diabetes and myopia.

Method 1 [MIM]: Machine inbuilt method (an automated algorithm supplied by the manufacturer, segments FAZ and calculates FAZ dimensions),

Method 2 [CEM]: clinical expert method (the FAZ border manually marked by a clinically experienced person. FAZ dimensions are calculated by inbuilt automated algorithm) and

Method 3 [NAM]: The new automated image processing technique. Here, the FAZ images were first processed by a DOG Filter iteratively 25 times after being complemented. This was followed by a Prewitt edge detection and repeated image dilation at angles of 0^0, 45^0 and 90^0. Image closure was then applied followed by noise and small object removal which resulted in the segmented boundary. For deeper insight into shape change, in addition to the diameter of the FAZ other parameters - area, diameter, major axis, minor axis, orientation, perimeter, F_{min}, F_{max}, Inner-circle radius, Circumcircle radius, orientation, vessel avascular density (VAD), Vessel diameter Index (VDI), vessel tortuosity was calculated. For further details please see the companion paper.[62] The circularity index was calculated using the area and perimeter parameters.[63]

3. RESULTS

All results are expressed as the mean ± standard deviation. The age, gender, best-corrected visual acuity, and the FAZ dimensions (area, diameter, major axis, minor axis, orientation, perimeter, F_{min}, F_{max}, Inner-circle radius, Circumcircle radius, orientation, VAD, VID and blood vessel tortuosity) were analyzed. The Best corrected Snellen visual acuity (BCVA) was converted to the logarithm of the minimum angle of resolution (logMAR). Variable normality was inspected using the Kolmogorov-Smirnov test. Comparisons between the three different methods and the degree of myopia and DM grades in diabetes were performed using the Student's t-test and one-way ANOVA. The Pearson correlation analysis was used to analyse the correlation between the FAZ area and the other parameters. We used the Bland-Altman plots to compare the FAZ area between NAM Vs. CEM and also NAM vs. MIM in normals (Figure 3), myopes (Figure 4) and DM (Figure 5).[64] In all analyses, p-Value < 0.05 was considered to be statistically significant. All the statistical analyses were performed using the SPSS software version 20 (SPSS, Inc, Chicago, IL).

A total of 328 children and adults with myopia and diabetes were included in the case group of this study. Ninety-four were clinically normal, 120 subjects with myopia and 114 were diagnosed with type II Diabetes Mellitus (DM) with and without Diabetic Retinopathy. The normal subjects mean ± SD age was 37.21 ± 17.09. The myopia group had a mean ± SD age was 26.62 ± 8.20. The DM group had a mean ± SD age was 56.84 ± 10.61. The basic demographic information for the subjects is shown in Table 3. The mean ± SD of FAZ area (mm^2) in normal, myopia and Diabetic Retinopathy by NAM and the other two methods are tabulated in Table 4. In normals, a statically significant difference was found between the methods ($p = 0.026$). The post-hoc analysis showed that the NAM and MIM results were significantly different ($p < 0.045$); however, no difference was found between the NAM vs. CEM groups ($p = 0.995$). In the myopic group, a statically significant difference was found between the methods (ANOVA $p < 0.018$). The post-hoc analyses showed that CEM vs. MIM results were significantly different ($p < 0.014$) but there was no difference between the NAM vs. CEM ($p = 0.720$) and NAM vs. MIM ($p = 0.286$).

Table 3: Demographic data and FAZ dimensions by NAM.

	Normals	DM	Myopia	Overall
Demographic data				
Sample Size	94	120	114	328
Mean Age ± SD	37.21 ± 17.09	26.62 ± 8.20	56.84 ± 10.61	40.29 ± 17.70
Gender Ratio (M:F)	69 : 25	51 : 69	68 : 46	193 : 141
Laterality (OD/OS)	50 / 44	62 / 58	58 / 56	170 / 158
MSE ± SD	0.25 ± 0.64	-4.31 ± 3.19	0.12 ± 1.56	-1.49 ± 3.07
Mean BCVA	-0.01 ± 0.04	-0.01 ± 0.04	0.22 ± 0.34	0.07 ± 0.23
FAZ dimensions by NAM				
Area (mm^2)	0.37 ± 0.09	0.46 ± 0.18	0.32 ± 0.08	
Diameter (mm)	0.68 ± 0.09	0.75 ± 0.14	0.63 ± 0.09	
Major axis (mm)	0.75 ± 0.11	0.87 ± 0.18	0.69 ± 0.10	
Minor axis (mm)	0.63 ± 0.09	0.68 ± 0.13	0.59 ± 0.09	
Perimeter (mm)	2.34 ± 0.36	2.91 ± 0.70	2.17 ± 0.33	
Eccentricity (mm)	0.07 ± 0.03	0.12 ± 0.05	0.07 ± 0.02	
F_{min} (mm)	0.63 ± 0.09	0.70 ± 0.14	0.59 ± 0.09	
F_{max} (mm)	0.79 ± 0.11	0.93 ± 0.18	0.73 ± 0.10	
Inner circle radius (mm)	0.29 ± 0.04	0.30 ± 0.06	0.27 ± 0.04	
Circumcircle radius (mm)	0.39 ± 0.06	0.47 ± 0.09	0.37 ± 0.05	
Orientation (^{0})	-3.24 ± 38.73	-2.20 ± 40.65	-1.51 ± 37.24	
VAD (dimensionless)	0.39 ± 0.05	0.48 ± 0.14	0.51 ± 0.11	
VID (mm)	28.94 ± 8.72	35.01 ± 10.52	30.15 ± 7.93	
Tortuosity (dimensionless)	1.44 ± 0.13	1.40 ± 0.09	1.49 ± 0.13	
Circularity (dimensionless)	0.84 ± 0.09	0.69 ± 0.15	0.83 ± 0.11	

The comparison of the mean ± SD of FAZ area (mm^2) for the myopic groups using the three methods is given in Table 5. The FAZ area shows reduced area in the high myopic group by CEM ($p = 0.004$) and MIM ($p = 0.008$). However, a statistically insignificant reduction found with NAM ($p = 0.169$). Similar to normals, the myopic FAZ area was smaller when computed using MIM.

Table 4: Comparison of FAZ Area by three methods in normals, myopia and Diabetes groups.

	FAZ Area (mm^2)				
	NAM	**CEM**	**MIM**	**p-Value***	**Post-hoc#**
Normals	0.37 ± 0.90	0.37 ± 0.10	0.33 ± 0.11	0.026	0.049 (NAM vs. MIM)
Myopia	0.33 ± 0.09	0.33 ± 0.09	0.29 ± 0.10	0.018	0.014 (CEM vs. MIM)
Diabetes	0.46 ± 0.18	0.47 ± 0.20	0.30 ± 0.15	0.000	0.000 (MIM vs. CEM & NAM)

*One-Way ANOVA #Bonferroni correction

Table 5: Comparison of FAZ area by three methods between Low-Moderate and High Myopia.

			FAZ Area (mm^2)		
	SE	**BCVA**	**NAM**	**CEM**	**MIM**
Low-Moderate Myopia	-3.54 ± 2.00	-0.01 ± 0.04	0.31 ± 0.10	0.33 ± 0.09	0.30 ± 0.10
High Myopia	-11.32 ± 3.57	0.03 ± 0.07	0.28 ± 0.08	0.25 ± 0.08	0.23 ± 0.07
Overall	**-4.31 ± 3.19**	**-0.01 ± 0.04**	**0.33 ± 0.09**	**0.33 ± 0.10**	**0.29 ± 0.10**
p-value	0.000	0.001	0.169	0.004	0.008

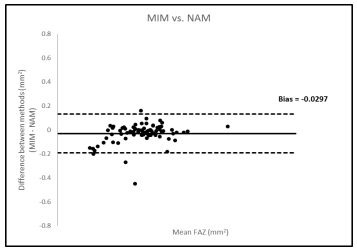
The FAZ area (mm^2) mean ± SD of in DM by all three methods are 0.46 ± 0.18, 0.46 ± 0.21 and 0.30 ± 0.15 using the NAM, CEM and MIM methods respectively. The perimeter mean ± SD (mm) of FAZ in DM by all three methods is 2.91 ± 0.70, 3.27 ± 0.82, 2.38 ± 0.73 using the NAM, CEM and MIM method respectively. The circularity index of FAZ in DM is 0.69 ± 0.15, 0.55 ± 0.09, 0.64 ± 0.11 with these three methods. Unlike normals and myopia, in DM groups also the MIM showed a larger FAZ area than the other two methods. The least circularity was found by CEM.

Table 6: Comparison of FAZ dimensions by three methods in based on severity of Diabetic Retinopathy.

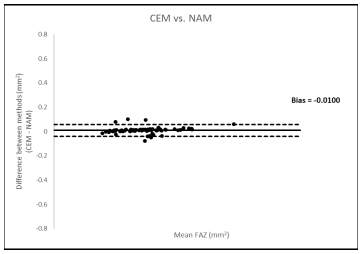
			FAZ Area (mm^2)		
	Age	**BCVA**	**NAM**	**CEM**	**MIM**
No DR & Mild NPDR	59.98 ± 11.02	0.09 ± 0.17	0.44 ± 0.15	0.43 ± 0.13	0.29 ± 0.14
Moderate NPDR	54.85 ± 08.81	0.21 ± 0.30	0.48 ± 0.19	0.49 ± 0.20	0.29 ± 0.17
Severe NPDR & PDR	54.42 ± 10.54	0.37 ± 0.43	0.47 ± 0.20	0.49 ± 0.26	0.31 ± 0.15
Overall	**56.79 ± 10.64**	**0.21 ± 0.33**	**0.46 ± 0.18**	**0.47 ± 0.20**	**0.30 ± 0.15**
p-Value#	**0.55**	**0.000**	**0.71**	**0.57**	**0.58**

#Kruskal Wallis Test

Bland-Altman analysis show that in all three conditions (normals in Figure 3 A & B, myopia in Figure 4 A & B and diabetes in Figure 5 A & B), the FAM showed a good agreement with CEM. However, the lowest bias was with myopes (Figure 4B). A low to poor agreement was shown between FAM vs. MIM and highest bias was shown with Diabetic Retinopathy (Figure 5A).

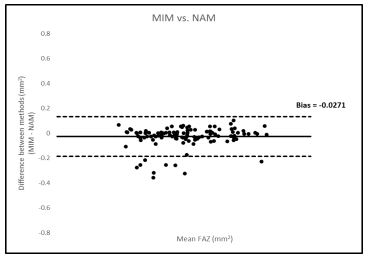


3.A

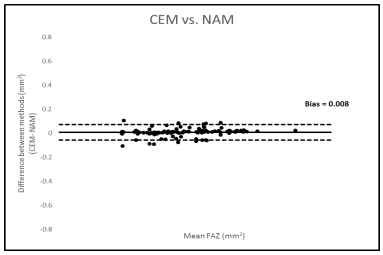


3.B

Figure 3: Agreement between the measurements methods in FAZ area for normals. A - MIM vs. NAM. B - CEM Vs. NAM.

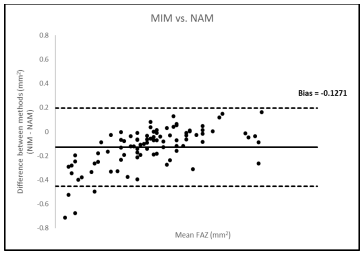


4.A

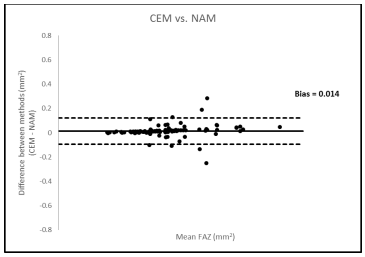


4.B

Figure 4: Agreement between the measurement methods in myopic FAZ area. A - MIM vs. NAM. B - CEM Vs. NAM.



5.A



5.B

Figure 5: Agreement between the measurements methods in Diabetes FAZ area. A - MIM vs. CEM. B - CEM Vs. NAM.

4. DISCUSSION AND CONCLUSIONS

The current study evaluated the accuracy of the new automated image processing technique, specifically designed for quantifying different FAZ dimensional parameters. The new method had good accuracy and agreement between all two methods. The CEM and MIM showed a mean error of 8.51% and the new method NAM showed good accuracy (the mean error 1.8%) on all the FAZ dimensions. Likewise, Figure 2 showed a good agreement was showed between method 2 (Manual) and method 3 (new automated method). To the best of our knowledge, this is the first study to validate the FAZ dimension including the area in normals and also in diabetes and myopes with a large dataset. We also have also compared with the results provided by the manufacturer's software (Zeiss CIRRUS 5000) and a clinical expert.

Our study results of the mean FAZ area is comparable to previous reports (Table 1). The Figure 6B shows the FAZ area in diabetics is significantly different compared to myopic eyes($p=0.003$) and normal eyes ($p=0.0016$). We found qualitatively that the area of the FAZ in diabetic retinopathy increased with increasing severity of the disease as shown in Figures 2 & 6B. In myopic cohorts (Figure 6A), our result showed a significant narrowing of the FAZ area in high myopes compared to low-moderate myopes contrary to other reports which showed an enlargement of the FAZ area. The current study is the first to quantify the orientation of major and minor axis. The orientation of the major axis of the FAZs in diabetes images was $1.85 \pm 39.65°$ which is close to the horizontal. In myopia and normal cases, orientations were $-8.29 \pm 34.00°$ and $-8.17 \pm 37.86°$.

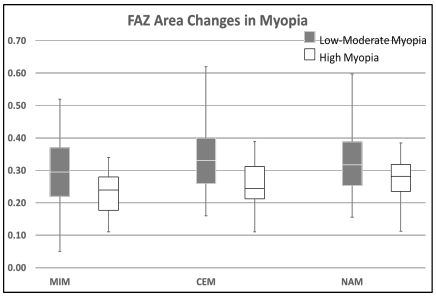


Figure 6A: A box-plot FAZ area variations in myopic.

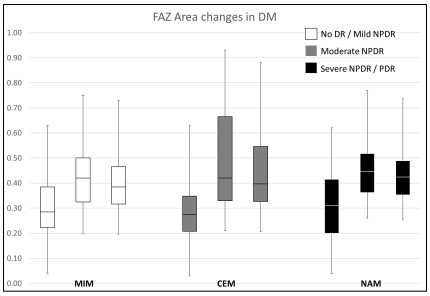


Figure 6B: A box-plot FAZ area variations in DM subjects.

OCTA provides the ability to quickly and non-invasively image the FAZ as well as to segment the superficial and deep layer retinal vascular networks[11]. Table 1 listed the FAZ area measurement in various studies using different imaging methods. Other than the OCTA, most of the FAZ imaging methods such as the FFA and AOSLO image both superficial and deep layers together and can't be separated. Over and above, the FFA method provides incomplete morphological information with superficial layer vascular network and even less information on deep capillary networks. Hence OCTA scores high when compared to other methods.

Multiple reports suggest that the FAZ in healthy eyes show high variability. Factors such as central retinal thickness, gender, SE, axial length and choroidal thickness influence the dimensions of the FAZ[20]. Furthermore, ocular media opacities especially cataract, small pupil size, blinking pattern and fixation instability during imaging also affect image quality. In about 3.03% of cases (0.33% in normal, 0.67 % in myopia and 2.02 % in DM) the manufacturer's inbuilt algorithm is unable to segment the FAZ zone. Table 7 shows the estimation error in calculating the FAZ area by different methods. The table shows that the MIM method underestimating the FAZ area about -9.40 % in normals and the underestimation increase both in myopia (-9.67 %) and DM eyes (-28.63 %). Hence, the method of segmenting the FAZ area might be another reason for variability.

Table 7: The estimation error in FAZ area by three different methods.

	(MIM-NAM)/NAM	(CEM-NAM)/NAM	(MIM-CEM)/CEM
Normal	***-9.84 %***	***-0.11 %***	***-9.40 %***
Myopia			
Low-Moderate	-6.74 %	3.70 %	-9.98 %
High Myopia	-13.00 %	-4.86 %	-6.89 %
Overall Myopia	***-7.39 %***	***2.83 %***	***-9.67 %***
Diabetes			
No DR / Mild NPDR	-28.18 %	0.84 %	-27.90 %
Moderate NPDR	-30.95 %	2.37 %	-32.27 %
Severe NPDR / PDR	-27.72 %	3.01 %	-29.98 %
Overall Diabetes	***-28.63 %***	***1.98 %***	***-29.64 %***

The Zeiss CIRRUS 5000 Angioplex system has the ability to provide five different parameters: two on vascular networks (vascular index and perfusion area) and three on FAZ dimensions (area, perimeter and circularity index). Because of the limited number of parameters, the information provided by the device limits our ability in differentiating diminutive pathologic foveal changes from normal age-related changes. The newer automated algorithm can provide a broader range of parameters, namely, diameter, major axis, minor axis, orientation, perimeter, F_{min}, F_{max}, Inner-circle radius, Circumcircle radius, orientation, VAD, VID and blood vessel tortuosity in order to quantitatively evaluate the FAZ and associated pathological changes since a larger dimensional parameter space is available.

A more sensitive myopia classification should be based on axial length and SE measures. Since this present study was retrospective, we had very few cases with axial length data. An important shortcoming is the unequal number of OCTA images for both high myopia and PDR conditions. We hope to further expand on the datasets as well as pathological conditions in future research. We are also developing a public database of FAZ images for other researchers.

In conclusion, our new automated method for determining the FAZ area was comparable to the clinical expert method. The new method gives additional FAZ dimensions when compared with the manufacturer's inbuilt algorithm. The FAZ area and circularity measurements given by the inbuilt algorithm are lower than that given by the new automated and clinical expert method. The new automated method can reduce the clinician's time in quantifying the FAZ. The detailed FAZ dimensions could potentially be used to further understand the development and progression/regression of retinal diseases.

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