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Research Article

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Papillary Trunk Bifurcation Angles as Major Determinants of Ocular Perfusion: A Cross-Sectional Study

Tabinda Hasan* **and Kavitha Ganesh**

Princess Nourah Bint Abdulrahman University, Riyadh, Saudi Arabia

*Corresponding author
Tabinda Hasan, Princess Nourah bint abdulrahman university, Riyadh, Saudi Arabia

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Abstract

Background: *Notable work has been done by Cecile and Murray in as early as 1926, on the structural and topological aspects of vasculature based on the concept that blood vessel size and arrangement is such that it provides blood flow with minimum energy loss. In the theoretical analysis of arterial networks, the existence of geometric optimisation for enabling functional adequacy has long been suggested, but observational studies have not yet fully corroborated these theories. Data on branching or bifurcation angles of retinal microvasculature is not only insufficient but also inconclusive.*

Aim: *Attending to this gap in information, we compared the central retinal artery (CRA) branching angles of known diabetics with healthy subjects and explored their possible role in determining the circulatory adequacy of human retina.*

Methods: *This study was done on North Indian subjects attending retina clinics of prominent tertiary centers of north India during 2019 through 2020. Fundus images were acquired through convenience sampling from 860 consecutive eyes of 430 subjects. Fluorescein fundus angiography was followed up for diabetics. CRA branching angles from digitalized fundus photographs of known diabetics and healthy subjects was analyzed through semi-automated digital image management tool and the readings were clinically correlated to note the occurrence and severity of retinopathic perfusion defects was*

Results: *We found marked differences between CRA branching angles among diabetics and healthy subjects and a significant correlation between branching anless and the occurrence and severity of retinopathic perfusion defects.*

Discussion and Conclusion: *The orientation of retinal blood vessels on the fundus plane is not merely 'a matter of chance' in the anatomic chronicle of the human body; rather, it has biological heralds and functional consequences. Direction, branching, angles; all determine the efficacy and abundance of blood flow in the human retina that hold indispensible relevance for optimal vision and might be subtle indicators of micro vascular damage in disease states. This study has elucidated retinal vascular geometrics of healthy and diseased Indians, a knowledge that can improve our understanding of 'abnormal features' and 'natural variants' in retinal vascular architecture. In this study, we quantified the 'structural factors' behind perfusion defects of the Diabetic retina.*

Introduction

Notable work has been done by Cecile and Murray in as early as 1926) on the structural and topological aspects of vasculature based on the concept that blood vessel size and arrangement is such that it provides blood flow with minimum energy loss. They even proposed that such morphological phenomenon embodies Poiseuille's law of flow and that the 'theoritical ideal bifurcation angle' should lie between 75 to 90 degrees. Studies on actual living humans show that arterial branch-angles are determined by unknown factors like branch vessel destination, biofeedback mechanisms and that the bifurcation angle follows the 'minimum energy hypothesis' but with 'significant scatter'. In the theoretical analysis of arterial networks, the existence of geometric optimisation for enabling functional adequacy has long been suggested, but observational studies have not yet fully corroborated these theories. Also, most angle studies have been confined to macrocirculation like coronary arteries Data on branching or bifurcation angles of retinal microvasculature is not only insufficient but also inconclusive. Attending to this gap in information, we compared the central retinal artery (CRA) branching angles from digitalized fundus photographs of known diabetics with healthy subjects through semi-automated software techniques and explored their possible role in determining the circulatory adequacy of human retina. Fluorescein fundus angiography was followed up for diabetics. We found marked differences between CRA branching angles among diabetics and healthy subjects and a significant correlation between branching anless and the occurrence and severity of retinopathic perfusion defects.

Methods

This study was done on North Indian subjects attending ophthalmology/ retina clinics of three prominent tertiary centers of north India including BHU hospital, Varanasi; Subharti hospital, Meerut; Sahara hospital, Lucknow during 2017 through 2019 as part of collaborative research program. Fundus images were acquired through convenience sampling from 860 consecutive eyes of 430 subjects (200 healthy and 230 diabetic; 310 males and 120 females, Mean age 46.80+-11.85; range 18-80 years). Individuals with history of ocular trauma or intraocular surgery within past 6 months, ocular inflammation or infection within the last 3 months, astigmatism more than +2.0 dioptres and ametropia of more than 65.0 dioptres were excluded. Stereoscopic color retinal photographs of two eyes with the optic disc well focused within half a disc size off the center were taken by mydriatic fundus camera (a table-mounted Topcon 50-EX digital camera and a PC-based image-management system) after pupil dilation with Phenylephrine Hydrochloride 10% and Tropicamide 1%.

Criteria for 'healthy' were absence of any fulminate medical condition, normal ophthalmic findings, especially normal appearance of the optic disc, normal visual fields, intraocular pressure and absence of retinal lesions. Persons were defined as having diabetes if they had a history of diabetes mellitus treated with insulin, intake of oral hypoglycemic agents and, or, a casual blood sugar of higher than 11.1 mM and a glycosylated hemoglobin≥ 48 mmol/mol as per the American diabetes association.

Diabetic patients with clear media, no history of allergic reactions and normal renal profile were selected for fundus fluorescein angiography in order to depict the 'presence' or 'absence' of perfusion defects (hypo-fluorescence or hyper-fluorescence) resulting from microcirculatiory blockade or leakage.

The direction of superior and inferior papillary trunks (the two terminal divisions of central retinal artery) were measured at their modal point on optic nerve head of digitalized fundus images and then considered as a summation function of the central retinal arterial bifurcation angle in a 360 degree fundus plane (Figure 1) gives an overview of the technique adopted) using semi-automated software (Bridge CS6 http:// www. adobe. com/ mena_ en/ products/ bridge. html) similar to what other researchers have used before. To avoid measurement bias, only fundus images showing terminal bifurcation of central retinal artery in front of lamina cribrosa were included in the study while those dividing behind were excluded (Figure 2).

Basic descriptive statistics (p value of significance <0.05 and confidence interval of 95%) was used to compare CRA bifurcation angles among diabetics and healthy. Dimorphism among eye sides and correlation with age were assessed. Association of CRA bifurcation angle with angiographic perfusion status was statistically evaluated for diabetics to elucidate structural factors behind functional defects after adjusting for potential confounding variables using multiple regression analysis. A further qualitative inspection of the angiographic reports was done by 3 trained opthalmologists to assess the severity of perfusion defects on a three point visual ratings scale (none /mild to moderate / severe). This impression was revisited in terms of corresponding CRA bifurcation angles of those subjects to elucidate any existing association between bifurcation angle values and the degree of perfusion defects that occurred.

Results

-A statistically significant correlation existed between CRA bifurcation angles and presence of angiographic perfusion defects (p<0.05) in the diabetic fundus (Table 1A).

- Wider CRA bifurcation angles increased the severity of microcirculatory lesions; as depicted by greater degree of angiographic perfusion defects on qualitative visual ratings scale. The trend observed was statistically significant (Table 1B).
- Diabetic eyes had considerably wider angles than healthy eyes (Table 2).
- The average CRA bifurcation angle was 161.41 degrees in healthy eyes and 216.24 degrees in diabetics (p<0.000) (Table 2).

-No difference existed between angle values across right and left eyes (Table 2) and there was no correlation with age; (p>0.1) for both diabetic and healthy subjects (Table 3).

Table 1 A: Angiographic perfusion status(mild vs. moderate vs. severe) for 197 out of 230 patients in the diabetic group who underwent fluorescein fundus angiography: north Indian subjects(N=430; 200 healthy ,230 diabetic) year 2019

Angiographic perfusion defects on qualitative visual gradings scale (n)	CRA bifurcation angle Mean+-SD	P value
None (85)	166+-21.90	< 0.05
Mild to Moderate (70)	221+-33.42	
Severe (42)	265+-31.97	

Table 1B: Correlation of angiographic perfusion defects (compromised microcirculation Mild vs. Moderate vs. Severe) with central retinal arterial bifurcation angles in north Indian subjects (N=430; 200 healthy; 230 diabetic)-2013

Angiographic perfusion status	Diabetic subjects (N=197)	Central retinal bifurcation angle Mean+-SD	P value
Perfusion defect present (mild to moderate to severe)	112	243+-32.83	<0.05*
Mild to Moderate (70)	221+-33.42	243+-32.83	
Severe (42)	265+-31.97	166+-21.90	

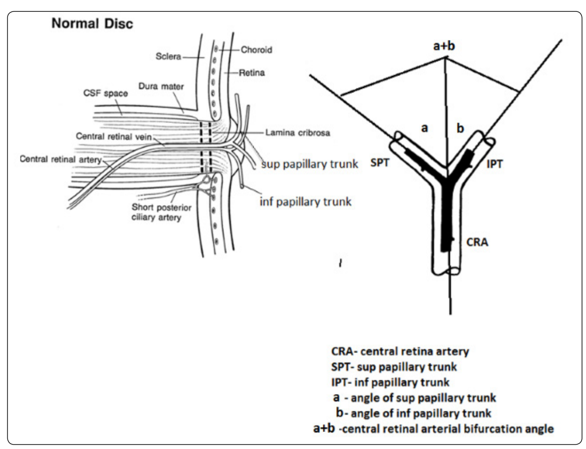

Figure 1A: Calculation of central retinal arterial bifurcation angle: The zero degree base line passing through the longitudinal axis of central retinal artery. The best straight lines passing through the papillary trunks were then considered for angulation with the central retinal axis. The central retinal arterial bifurcation angle was calculated as a summation function of the sup and in papillary trunk angles.

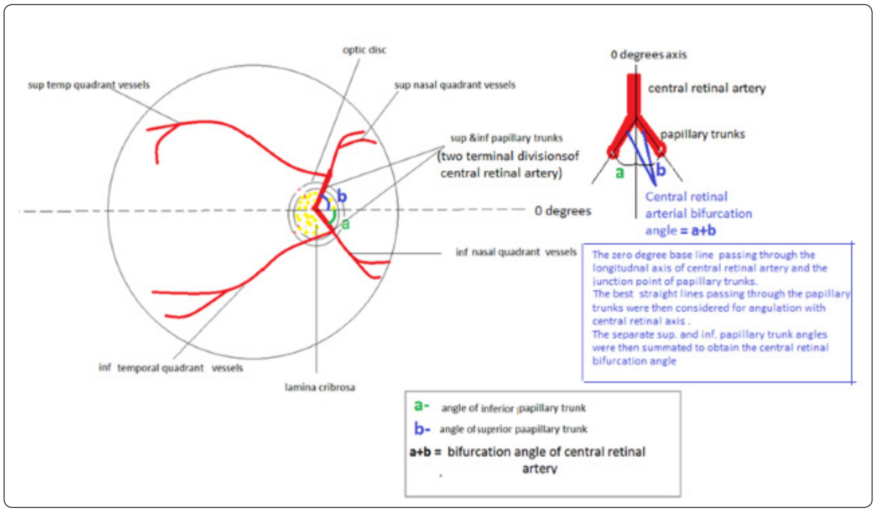

Figure 1 B: Bifurcation angle of central retinal artery calculated as summation function of angles of superior and inferior papillary trunks

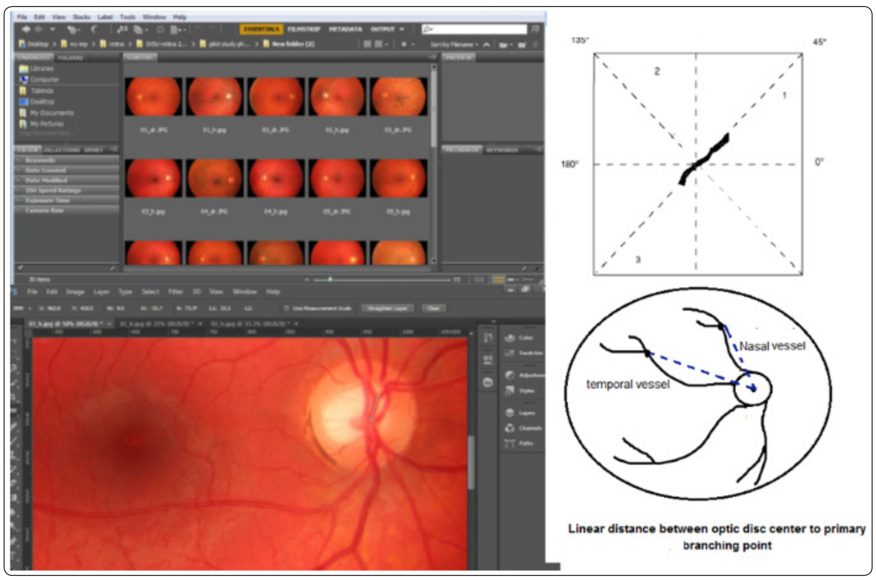

Figure 2: Calculation of papillary trunk and retinal artery bifurcation angles on bridge CS 6 digital image management software

Table 2: Comparison of papillary trunk direction and CRA bifurcation angles in both eyes of north Indian subjects (N=430; 200 healthy, 230 diabetic) year 2019

Status (n)	Superior papillary trunk direction Mean+-SD		Inferior papillary trunk direction Mean+-SD		CRA bifurcation angle Mean+-SD		P value Right vs Left eyes (paired t test)	Mean CRA bifurcation angle	P value Diabetic vs. Healthy (anova)
	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye			
Healthy (n=200)	80.85+-28.61	79.90+-20.21	82.34+-25.35	79.23+-20.32	163.69+-26.98	159.13+-23.02	>0.1	161.41	<0.000*
Diabetic (n=230)	101.88+-42.32	106.26+- 7.66	111.34+-35.86	113.03+-40.59	213.22+-38.92	219.29+-46.43		216.24	

* p value highly significant

Table 3: Correlations with age- north indian subjects (N=430; 200 healthy; 230 diabetic)-2019.

Medical status (n)	Central retinal artery bifurcation angle (in degrees)	Correlation with age (Pearson coefficient)	Significance (p value)
Diabetics (230)	161.41	.170	.172
Healthy (200)	216.24	.215	.083

*P value significant

Discussion

Branching angle (in degrees) represents the angle between two daughter vessels and is related to blood flow efficiency, energy cost of bulk flow and diffusion distance An optimal arterial branching angle is associated with greater competence in blood flow with lower amount of energy spent by the body. Researchers propose that the optimal value for branching angle is 75 degrees and increased angles have been related to decreased blood flow [1-3].

In this study, central retinal arterial branching angle which is significantly more than the value (75degrees) suggested by Tarnhoj in 2006 [4]. One possible explanation for this discrepancy may be that the value quoted by Tarnhoj et al. pertains to smaller arteriolar subdivisions further down the retinal vascular tree (mainly tertiary or quarternary level branches) whereas the central retinal artery branching angle (as reflected by papillary trunk directions measured during the course of this research) pertains to a relatively 'huge' primary vessel of retinal circulation basically present at the root of the arterial tree and hence, it might seem logical that flow dynamics and architectural properties of wider and bigger vessel tubes may not necessarily follow the same principal as smaller arterioles further down the subdivision chain. Another possible, but weaker explanation of such divergence may lie in the proven demographic, genetic and heredity influences on retinal vascular geometrics which may account for the morphological differences observed in different study populations.

Decreased arterial branching angle has previously been associated with ageing and hypertension. In this study, we found that advancing age presents with increased or wider superior papillary trunk angles which simultaneously translates into decreased or narrow central retinal artery branching angles, thereby agreeing with previous researchers. Some researchers have found increasing diabetes duration associated with increased arteriolar angles, findings supported by our results where wide papillary arterial trunk angles were associated with diabetes [1, 5-7].

Theoretical as well as experimental works support the concept that the vascular architecture of our body develops in a way that is optimized for efficient blood flow and that deviations from this optimal state occur in disease processes. The retinal microcirculation is no different. Bifurcation angle is referred to as the angle between two daughter vessels at the vas¬cular junction and as per Murray's law; the most competent circula¬tion across a vascular network can be achieved if blood flow is proportional to the cubed power of the vessel's radius [8]. Studies have shown that acute angles are optimal at arteries and arterioles bifurcation in terms of circulatory dynamics.

This functional adequacy of acute angles of arteries in circulation was further confirmed in the present study where narrower papillary trunks angles (less than 90 degrees) were associated with better angiographic perfusion status of retinal microcirculation. Retinal arteriolar bifurcation angles have been found to be reduced in hyper¬tension and low birth weight males. In this study, bifurcation of central retinal artery into superior and inferior papillary trunks had narrower angles in hypertensives as compared to healthy as well as diabetic subjects, particularly for the right eyes. Growing Up in Singapore towards Healthy Outcomes Study (GUSTHO) reported that maternal blood pressure during mid pregnancy had an impact on retinal microcirculation among pregnant Asian women of young to middle age group [9, 10]. Elevated blood pressure was associated with a range of retinal arteriolar changes in women during pregnancy. Retinal vascular parameters were measured by a semi-automated computer-based program which observed that every 10-mm Hg increase in mean arterial blood pressure was associated with a 0.9° reduction in retinal arteriolar branching angle, a 1.9-µm reduction in retinal arteriolar caliber and a 0.07 reduction in retinal arteriolar fractal dimension, respectively all of which were highly statistically significant findings [7].

As compared to the findings of GUSTHO, the present study observed blood pressure being inversely related to papillary trunk angles; superior papillary trunk was 80 degrees in healthy subjects and 74 degrees in hypertensives while the inferior papillary trunk was 90 degrees in healthy subjects and 54 degrees in hypertensives for right eyes of both males and females. Alternatively, in context of branching or bifurcation angles, one can state that the central retinal arterial bifurcation angle increases as the blood pressure levels increase as was observed in this research where the narrowing of papillary trunk angles during hypertension arithmetically translated into widening of central retinal arterial branching angles. The altered flow dynamics in the scenario of an elevated systemic blood pressure might cause papillary trunks to become oriented at sharper angles as part of the body's auto regulatory mechanism; but exactly 'how' this occurs and how it might be affecting the natural homeostasis remains unclear and is beyond the scope of the present research. In another related study, the average arteriole bifur¬cation angle was 70.1° with an average of 69.8° for men and 70.5° for women [11].

The present study individually recorded the angular values for central retinal arterial bifurcation into superior and inferior papillary trunks. The superior papillary trunk direction was as acute angled in all healthy fundus; (80 degrees); which is about 10 degree more than the values recorded by Michael E and his team in 2012; while the inferior papillary trunk was right angled / 90 degrees at the optic disc in retina which again is greater than the value recorded by Michael and co-workers [12]. The right superior papillary trunk direction among hypertensives was more comparable to normal healthy values, while the diabetic fundus showed highest obtuse angle values. The left superior papillary trunk angulation was about 20 % narrower in healthy fundus as compared to diabetic and hypertensive fundus. While Michael stated that for arteriole bifurcation, no significant difference between left and right eyes or genders occurred; our study showed statistically significant difference between the two eyes regarding central retinal artery bifurcation angles as objectively perceived by differential records of superior and inferior papillary trunk angles. The angulation of superior and inferior papillary trunks of both eyes did not vary among genders, findings that match those of Michael et al [12-14].

It has been detected that vessel angles can change up to 50° due to local changes in blood flow. In the present study, superior papillary trunk angles increased by 15 degrees in cases of increased blood pressure. Previous studies have shown a reduction in the arteriolar bifurcation angles associated with advancing age [13-15]. Our study showed wider angles of papillary trunks with advancing age and the change was highly significant for superior papillary trunks. This alternatively means reduced central retinal arterial bifurcation angles in the elderly; findings that agree with Stanton et al. This study also exhibited a significant proneness to fluorescene angiographic perfusion defects upon widening of superior papillary trunk angles by as little as 10 degrees. These two findings seem all the more logical and one supports the authenticity of the other; considering that old age leads to widening of arterial trunk angles and widening of angles causes impaired microcirculatory function visible upon angiography as perfusion defects that characteristically mark the geriatric failing of oculo-visual functions. However, there is a need for large-scale studies to objectively corroborate with our results and further investigate the mechanistic link between retinal vascular metrics and perfusion profiles. Further studies on the subject may provide an insight into how these biomarkers change in health and disease, and how they may be used as a surrogate indicator in the intervention of systemic disorders.

We observed a great range in central retinal arterial bifurcation patterns as reflected by varying papillary trunk angles; a finding that is unlikely to be due to software error such as ones encountered previously [15, 16]. These varying angles sup¬port prior records of wide variations having been observed at retinal arteriolar bifurcation points. The physical changes that occur with increasing age at arterial bifurcation points i.e. reduction in angles with advancing age as recorded by others are similar to what we observed in our study of the papillary trunk angles at the central retinal arterial bifurcation point [17-20].

The orientation of retinal blood vessels in the fundal plane is not just 'a matter of chance' in the anatomic chronicle of the human body; rather, it has physiological insinuations coupled with morphological and functional implications. The direction of blood vessels determines the efficacy and abundance of blood flow in the human retina that holds indispensible relevance for optimal vision. Our study elucidated the superior papillary trunk direction as a determinant of microcirculatory perfusion status. Previously, the clinical relevance of retinal vessel directions has been stated by previous researchers. These researchers proved that the position of main retinal blood vessels correlates with Retinal Nerve Fiber Layer thickness profiles. A negative correlation was found between both superior and inferior angle and the super temporal and inferotemporal Retinal Nerve Fiber Layer thickness, and a positive correlation between both angles and super nasal and infer nasal Retinal Nerve Fiber Layer thickness [6]. This correlation might improve the diagnostic power of Nerve Fiber Layer measurements as a test for marking the extent of glaucomatous damage. Our results have yet again elucidated the clinical significance of retinal vascular directions; we have shown an unexpected but definite association between papillary trunk angles, age, disease states and microcirculatory perfusion status. Since no other study has investigated this relationship before, further research would be welcome to endorse and enhance these findings. Therefore, we suggest more exploration into the functional and clinical relevance of papillary vascular trunk orientation.

A major difficulty in this field is the lack of experimental or observational data. It is not an easy matter to measure the diameters and branching angles of blood vessels in vivo, and if the vessels are removed, from the body it is not easy to avoid some changes in their diameters and branching angles in the process. These difficulties are compounded by the need for a sufficiently large amount of data to provide good statistical evidence. Zamir and his team obtained a set of such data from photographs of arterial bifurcations in the human retina [21]. The results gave good support to the theoretical predictions but the data were characterized by a considerable amount of scatter.

The presence of wider angles at papillary trunk of the arterial tree in diabetics as compared to hypertensives or healthy subjects probably accounts for the relatively more severe perfusion defects observed during qualitative inspection of diabetic retinopathy fundus of our study. Alternatively, narrow papillary trunk angles observed in hypertensives makes them morphologically 'more comparable' to healthy fundus. This perhaps accounts for their 'less severe' angiographic perfusion findings as observed during this study as compared to others [22, 23].

In a nutshell, microcirculation of the human retina is majorly determined by prime morphological factors: like, the direction of papillary trunk as it emerges from the disc. 'Sharp angles' arry better prognosis. Overall, superior quadrant vessels; namely superior papillary trunk, (in terms of direction) and superior temporal artery, (in terms of prime bifurcation distance) are significant morphological determinants of perfusion status in retinal microcirculation. Hence, individuals with naturally occurring wide angled papillary trunks might be structurally more prone towards the development and progression of microcirculatory perfusion defects. Increased angles of papillary trunks in old age, diabetes and hypertension augment susceptibility for retinopathy lesions. The distinct patho-physiological processes and anatomic ultra-structural adaptations and alterations that mirror health conditions and numerous disease states are unique to the human retina [24-26]. Although 'which event precedes the other' or 'whether these occur in concomitant rhythm' still remains to be objectively explored.

The morphology of retinal blood vessels in the North Indian population is not so different from other populations except for a few intuitive parameters, particularly angulation and branching patterns, which seems natural owing to proven demographic and genetic influences on retinal vascular morphology. Broadly stating, the healthy fundus has d its superior papillary trunks are positioned at keener angles than inferior trunks. A certain degree of dimorphism exists among eye sides ers; a finding that appears quite consistent morphologically. We presume that the natural dimorphism of retinal vasculature as observed in this study might underlie unequal rates of progression of retinal lesions within two eyes of an individual or among 'seemingly comparable' individuals, even though the exact mechanism for this remains unclear.

Conclusion

The orientation of retinal blood vessels on the fundus plane is not merely 'a matter of chance' in the anatomic chronicle of the human body; rather, it has biological heralds and functional consequences. Direction, branching, angles and tortuosity, all determine the efficacy and abundance of blood flow in the human retina that hold indispensible relevance for optimal vision and might be subtle indicators of micro vascular damage in disease states. This study has elucidated retinal vascular geometrics of healthy Indians, a knowledge that can improve our understanding of 'normal features' and 'natural variants' in retinal vascular architecture. In this study, we quantified the 'structural factors' behind perfusion defects of the Diabetic retina. Our proposed approach, owing to its simple and direct application, has good reproducibility and can be further exploited for algorithm based temporal analysis of retinal vasculature in health and in disease states. Such an in depth morphological knowledge will facilitate an understanding of the pathogenesis of various disease phenomenon mirrored in early retinal changes and aid in planning timely and effective interventions. Upon decoding the 'type' of morphological changes leading to perfusion defects, we can plan to better identify 'at risk' individuals during screening programs and perhaps even think of designing biologically feasible intervention measures to alter or delay these events through 'site targeted' interventions. The potential utility of diagnostic and predictive fundus vascular screening for appraisal of health risks in populations is a worthwhile direction to explore and can lead to remarkable logistic savings. It needs to be comprehensively tackled in prospective studies in order to be used as a time and cost effective clinical tool for Indian ophthalmologists during upcoming years.

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