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Are foveal avascular zone and macular vessel parameters different, pre and post dilatation in diabetes?

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Abstract:

Introduction: Optical coherence tomography and optical coherence tomography angiography are ancillary tests done in an ophthalmological examination to observe the structural and functional state of retinal vasculature. Diabetes mellitus affects these vessels, and tests are often done in the dilated eye for precise images. The effect of mydriatic drops, which are used for this purpose, on the macular vasculature of retinopathic eyes has not been evaluated, and an existing change could alter the pathological assessment of macular vasculature.

Material and methods: We evaluated the effect of dilating drugs on vessel density, perfusion, and foveal avascular zone, which may reflect an altered vascular picture, and thus a deviation from the non-dilated vascular status of the macula.

We assessed 60 eyes in our cross-sectional study as per Inclusion and exclusion criteria, (diabetics with retinopathy, without retinopathy, and non-diabetics). Optical coherence tomography and optical coherence tomography angiography were performed in all eyes before and after mydriasis. The pre- and post-mydriatic values for each macular zones were analysed.

Results: The centre, inner, and full zones of the macula of diabetics with and without retinopathy and the controls were analysed for vessel density and perfusion. The Wilcoxon signed rank test was employed. Significant changes in VD and VP were noticed after dilatation with retinopathy. The macular vasculature of non-diabetics and diabetics without retinopathy, except for the central zone, remained unchanged. Foveal avascular zone remained insignificant.

Conclusions: This study discloses the effect of mydriatic drops on vessel density and perfusion of macular vessels among diabetics. To delineate the true vascular status of the macula of an eye with retinopathy, optical coherence tomography angiography in an undilated eye would be desirable.

Key words: diabetic retinopathy (DR), dilatation, macular vasculature, vessel perfusion (VP), vessel density (VD), foveal avascular zone (FAZ).

Introduction

Pupillary dilation can yield high-quality optical coherence tomography (OCT) images when the retina and choroid are evaluated. Typically, an OCT angiogram is done on a patient in mydriatic state. The drug commonly used for this is a combination of 0.8% tropicamide (C17 H20 N2O2) – a benzene acetamide Para sympatholytic that blocks the M4 muscarinic acetylcholine receptor – and 5% phenylephrine – an α1 adrenergic receptor agonist that induces vasoconstrictive activity. Both these drugs have an effect on retinal capillary perfusion [1, 2].

OCT is an ancillary test that has become an indispensable tool for anterior and posterior segment evaluation. Although not substitutable, OCT angiography (OCTA) is often preferred over fluorescent angiography because of its high-resolution imaging capabilities, potential to detect changes in the microvasculature, reliability, reproducibility, and non-invasiveness. Angiographic studies using this device have importance in evaluating the macula, both for ocular and systemic diseases, of which diabetes mellitus predominates, with many ocular complications. Out of an estimated 285 million people worldwide with diabetes mellitus, approximately one third display signs of diabetic retinopathy (DR). Amongst them, a further one third have vision-threatening DR, which includes diabetic macular oedema (DME).

The foveal avascular zone (FAZ) is a region of the human retina with the highest cone photoreceptor cell density, and it is completely devoid of retinal capillaries. This is an area that is peculiarly susceptible to diabetic complications. Because the pupillary dilating drops are shown to reduce the retinal vessel density [3–5] in the parapapillary zone, if such an effect also exists in the macular area, angiography of the macula after dilatation might not show the true vascular status of this region. A drug-induced change in the vascular status of the macula has not been established unequivocally.

The pre- and post-mydriatic vessel density and perfusion of the macula between normal subjects and diabetics with and without retinal changes have not been angiographically compared prior. Hence, the assessment of maculae of the above three groups are evaluated herein for changes in vascular calibre that the dilating drugs might affect.

Material and methods

This cross-sectional study was approved by the Institutional Review Board (Approval # IEC / 2024/03/402) and performed by conforming to the principles outlined in the Declaration of Helsinki. Written informed consent was provided by each participant, and the study was explained to them in detail, including the infrequently observed possibility of hypersensitivity to topical medications. All the subjects were healthy, non-smoking, and normotensive. None of them were on any ophthalmic treatment nor on any medication that could alter autonomic, cardiac, or vascular functions. Eyes with macular oedema, glaucoma, past vitreo-retinal surgery, uveitis, and an axial length exceeding 26 mm were excluded. Any conditions impeding the media clarity like corneal opacities, cataract, and vitreous haemorrhage that could prevent high-quality OCT images were also omitted.

The participants were within the age group of 30–70 years. They were enrolled between December 2023 and January 2024. All the participants underwent complete ophthalmic evaluation including assessment of best corrected visual acuity with Snellen's chart at a distance of 6 metres, slit lamp bio-microscopy (Carl Zeiss model SL 115 Classic), non-contact tonometry (TOPCON CT -IP), axial length measurement (IOL master 500 Zeiss Germany), and refraction. Undilated fundus examination was done in all participants to assess the posterior segment, including the macula. Baseline OCT and OCTA imaging were done in all who were included in the study. After acquiring these scans, drugs employed to dilate the pupils were instilled – a mixture of 0.8% tropicamide, a parasympatholytic, and 5% phenylephrine, a sympathomimetic – one drop 3 times with an interval of 10 minutes. Thirty minutes after application of the initial drop, each participant was subjected to undergo OCT/OCTA in the mydriatic state with a Zeiss Cirrus 5000- HD OCT.

The Zeiss Cirrus HD OCT 5000 has a scan speed of 30,000-70,000 A scans per second. These image frames capture the intensity of speckled patterns during each scan, and these patterns vary in each frame because of the movement of light-scattering particles, which are erythrocytes in this scenario. Surrounding this erythrocyte movement, i.e. the blood flow, are the vessels and tissues that are static. Hence, there exists a decorrelation between the tissue that flows and tissue that is static. The slightest difference between the speckled pattern images, together with the decorrelation, form the phenomena on which the OCTA is based.

Vessel density (VD)

Vessel density is defined as the total length of perfused vasculature per unit area in the region of measurement of the superficial layer, where the vessel density is more, than deep, that extends from the internal limiting membrane (ILM) to 15 microns below the inner plexiform layer (IPL). This measurement, which is displayed automatically in the printout, quantifies the density of blood vessels within the macular region by evaluating the area filled with flowing blood, in an OCT (Fig. 1).

Vessel perfusion (VP)

Vessel perfusion refers to the measurement of blood flow within the macular region. The OCTA image in figure 2 details the perfusion in the central, inner, and full regions (Fig. 2).

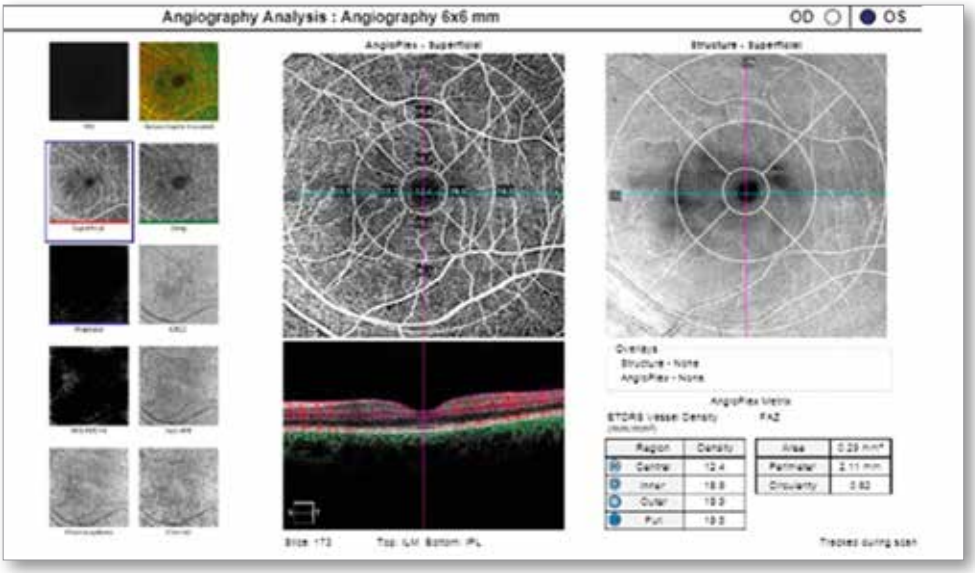

Fig. 1. OCTA with vessel density of the central, inner and full regions.

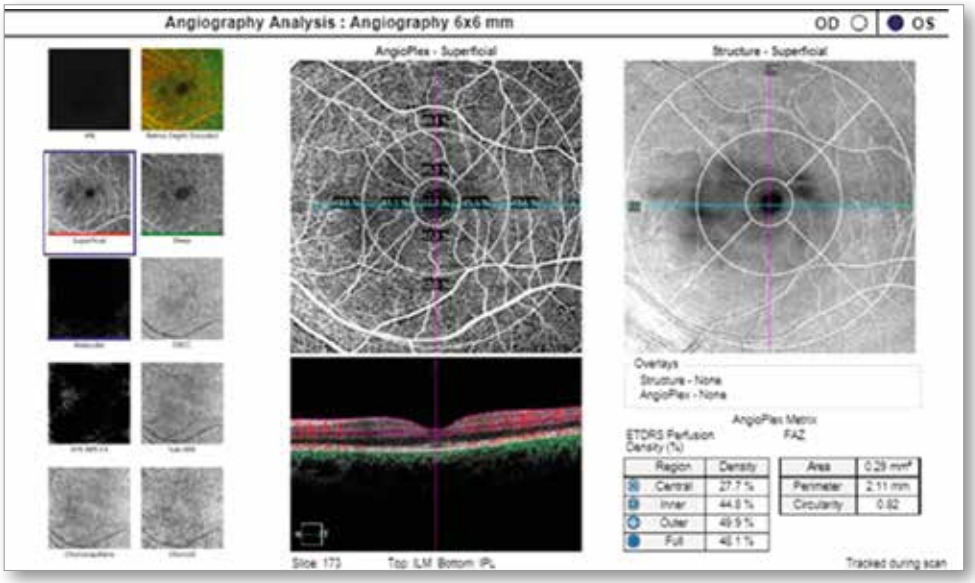

Fig. 2. OCTA with Vessel Perfusion of the central, inner and full regions.

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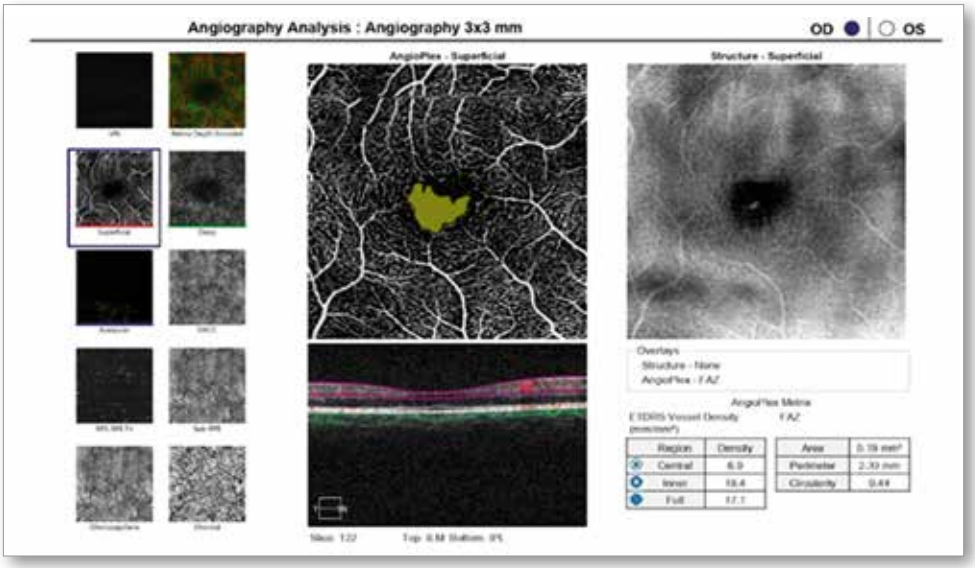


Fig. 3. OCTA image of FAZ.

FAZ is defined as a region approximately 0.5 mm in diameter in the centre of the retina that lacks blood vessels. The size of this area can vary in various systemic disorders, primarily those affecting retinal vasculature. Because the FAZ is delineated well with an OCTA 3 × 3 mm protocol than with 6 × 6 mm, probably due to its higher scan density, the former was employed in this study. FAZ can be obtained either from the density or the perfusion display (Fig. 3).

All the above parameters were measured by automated software that ensures that the measurements will be objective, reproducible, and free of observer bias.

Statistical analysis

The statistical analyses were performed with a statistical software package, SPSS version 22.0. The Wilcoxon test was employed to stratify the changes in mean vessel density, vessel perfusion, and FAZ before and after applying the dilating drugs in diabetics and non-diabetics. The diabetics were further stratified as those with and without retinopathy, and variations in the above variables were analysed.

Results

Out of the total 60 eyes that were enrolled in the study, 24 belonged to males and 36 to females within the age range 30 to 70 years. Forty-three of these eyes were from diabetics (71.66%) with 33 of them having no retinopathy (76.74%), 4 with mild non-proliferative changes (9.30%), 5 with moderate non- proliferative changes (11.62%), and 1 with severe non-proliferative changes without macular oedema or ischaemia (2.32%). Seventeen participants that enrolled were non-diabetics.

Vessel density (VD)

It was observed that no significant changes were seen in VD (except for DM without retinopathy-centre zone) among the control group and diabetic patients without retinopathy before and after dilatation. In patients with diabetic retinopathy, there was a significant change in VD in all the three zones – the centre (p=0.011), inner (p=0.005), and full (p=0.005) (Tab. I).

Similar to the VD findings, no significant changes were seen in the control group and diabetic patients without retinopathy (except for DM without retinopathy-centre zone), but in diabetics with retinopathy, the centre, inner, and full zones showed significant variations, centre (p=0.022), inner (p=0.008), and full (p=0.005), respectively (Tab. II).

Group	Zone	Pre dilatation	Post dilatation	Z- value	p- value
Controls n=17	Centre	7.13±2.79	7.31±4.35	0.517	0.605
	Inner	18.06±2.71	18.05±3.31	0.233	0.816
	Full	16.80±2.64	16.85±3.33	0.181	0.856
DM without retinopathy n=33	Centre	6.86±2.56	7.46±3.22	2.118	**0.034**
	Inner	18.05±2.32	18.05±4.09	0.652	0.514
	Full	16.82±2.19	16.95±3.54	0.786	0.432
DM with retinopathy n=10	Centre	5.80±1.91	6.95±1.62	2.552	**0.011**
	Inner	17.99±1.31	19.05±1.21	2.805	**0.005**
	Full	16.64±1.22	17.70±1.17	2.803	**0.005**

Tab. I. Vessel density in controls, DM without retinopathy and DM with retinopathy.

Group	Zone	Pre dilatation	Post dilatation	Z value	p- value
Controls	Centre	12.44± 4.93	12.51±7.35	0.450	0.653
	Inner	33.02±4.40	31.56±6.94	0.970	0.332
	Full	30.69±4.34	29.28±6.89	0.971	0.332
DM without retinopathy	Centre	12.08±4.62	13.13±5.39	1.975	**0.048**
	Inner	33.40±3.73	33.14±6.84	0.465	0.642
	Full	31.07±3.69	31.1±5.67	0.572	0.567
DM with retinopathy	Centre	10.52±3.66	12.66±3.04	2.295	**0.022**
	Inner	33.66±2.63	35.58±1.90	2.668	**0.008**
	Full	31.11±2.77	33.25±2.49	2.805	**0.005**

Tab. II. Vessel perfusion in controls, DM without retinopathy and with retinopathy.

It was interesting to note that significant changes were observed before and after dilatation for VD and VP, in the central zone of diabetics without retinopathy, while the inner and full zones remained unchanged, probably expressing the vulnerability of this zone for the initial pathological disturbance in autoregulation before progressing to a global macular perfusion dysregulation.

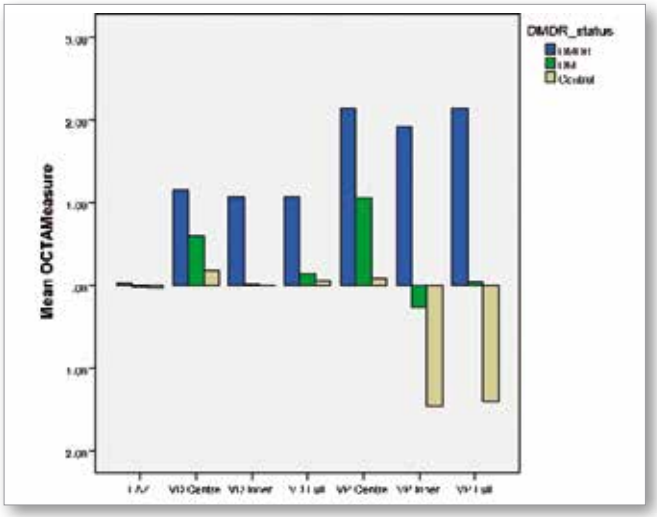
Foveal avascular zone (FAZ)

The foveal avascular zone was analysed in all the sub-groups before and after instilling the mydriatic drugs for a change in the area. Both the controls and diabetics without retinal changes did not show any differences, but diabetics with retinopathy exhibited a mild increase that was not significant (p=0.096) (Tab. III).

	Pre- dilatation	Post-dilatation	Z Value	p-value
Controls	0.21 ± 0.18	0.18 ± 0.16	0.648	0.517
DM without DR	0.21 ± 0.15	0.19 ± 0.15	0.657	0.511
DM with DR	0.23 ± 0.11	0.25 ± 0.16	0.119	0.906

Tab. III. FAZ area in subgroups.

The bar graph illustrates the pre-dilatation and post-dilatation changes observed in vessel density and vessel perfusion. The foveal avascular zone did not show any appreciable change.



In addition, the Kruskal-Wallis non-parametric test was employed to analyse the vessel density (VD) and vessel perfusion (VP) in non-diabetics, and diabetics without retinopathy and with retinopathy. No significant differences were observed between the three groups, but significant changes in VP were observed in the inner and full region (p=0.015 and 0.014, respectively) for diabetics with retinopathy.

Discussion

This cross-sectional observational study, in which tropicamide and phenylephrine were used, did not show any change in perfusion or density of the macular network of vessels in the controls and diabetic patients with no clinical evidence of retinopathy, before and after administering the drug. Contrary to this, an increase in vessel density and perfusion, after administering the drug, were noticed in the macular vasculature of eyes with diabetic retinopathy.

The aforementioned mydriatics were used previously to evaluate their action on macular blood flow that was based on the flow of white blood cells in the macular capillaries with inconclusive results. White blood cells, which travel much slower than red blood cells in the retinal capillary system, may not manifest an appreciable change in velocity when compared to that of red blood cells. Hence, OCTA is based on the movement of RBC that clearly portrays the vessels of the retina.

Both phenylephrine and tropicamide were used topically to bring about maximum dilation of pupils to improve OCTA image quality. Earlier studies of these drugs on macular vasculature did not appear to have any effect on the vessel density or perfusion, but their effects on functionally compromised vessels, as in diabetic retinopathy, has not been previously evaluated.

The preparation of the specified mixture, phenylephrine and tropicamide, as above, was used as mydriatics and applied topically. Topically applied drugs can reach posterior peri-ocular tissue and the posterior retina by permeating through the sclera and choroid to reach the photoreceptors and neural retina [6]. Antiglaucoma drugs dorzolamide, brimonidine, and betaxolol were largely distributed in posterior segment tissues as well as dexamethasone and nepafenac [7] after topical application.

Drug permeability of the sclera is comparable to that of the cornea. Furthermore, it has been observed that the sclera is independent of lipophilicity [8]. These properties of the ocular tissue aid in the transport of drugs that are instilled into the conjunctival sac. Tropicamide is a drug that has maximum transport across the cornea [8]. In diabetics, this transfer occurs more as observed in the experimental studies, and the disruption of the blood retinal barrier may enhance this [9]. Retinal vessels do not have autonomic innervation and thus are not overseen by the central nervous system [10]. Distal to the lamina cribrosa, these vessels are autoregulated, especially the capillaries of human macula [11].

The local autoregulation is controlled by the pericytes on the capillary walls and smooth muscles of retinal arterioles [11]. These pericytes have been shown to respond in the presence of vasoactive substances. Because the highest concentration of pericytes are seen in the retinal microvasculature [12], its activity should be of great importance in the autoregulatory functions of retinal vessels. The resting tone of these pericytes keeps the capillaries in a relaxed and dilated state – perhaps EP4 receptor-mediated. The presence of acetylcholine (ACh) binding sites for muscarinic receptors on pericytes confirms its contractile nature, which, when activated, results in vasoconstriction. The source of this ACh is uncertain. However, starburst amacrine cells, although located far from the cholinergic receptors are found to release this [13] and could contribute to this effect. Another possible source of ACh is the blood vessels themselves because choline acetyltransferase, the rate-limiting enzyme in the synthesis of ACh, is detected within. ACh thus released is believed to reach the effector sites either through diffusion or volume transfer.

Vascular smooth muscles of arterioles are dependent on Nitric Oxide (NO) for its relaxation. The release of NO from the endothelial cells is mediated by ACh [13]. It is also found that the arteriolar smooth muscle relaxation by NO is regulated by NO synthase, and pericytes have a control in its expression [14]. The smooth muscle relaxation was found to be more responsible for hyperaemic changes in the retinal vasculature than pericytic activity alone.

The passive nature of the posterior retinal vessels within the macula towards phenylephrine could be explained based on its affinity to a specific receptor. This drug, an alpha 1 agonist, needs to have alpha 1 adrenergic receptors to accomplish its activity. These receptors are present in the relatively large vessels in the parapapillary area [15], hence the constriction of these vessels, unlike the macular arterioles that lodge alpha 2 receptors [16] on which phenylephrine remains ineffective. Phenylephrine, in the posterior periocular tissue, has a close adjacency with the short

posterior ciliary arteries, the twigs of which supply the optic nerve head. The vasoconstrictive response of these vessels is thus observed around the parapapillary area, unlike the macular vessels, which are terminal branches of the central retinal artery that pierces the optic nerve approximately 10 mm from the sclera, thus being less proximal to the site of drug concentration. The drug could also pass into the eye and affect the retinal vessels directly.

In our study on the response of macular vasculature in the controls and diabetics with no retinopathy to a topical phenylephrine tropicamide combination, contrary to its effect at the parapapillary area, did not show any significant changes in the macula, and this was consistent with similar previous studies [7]. After dilation in the diabetic retinopathy subgroup, an increase in FAZ was noticed that was not significant. However, the vessel density in the centre, inner, and full areas of the macula in diabetic retinopathy subgroups exhibited a considerable increase after topical medication while the other subgroups remained unaffected. Vessel perfusion in the centre, inner, and full zones displayed an increase in perfusion after topical administration of the drug, although the other subgroups did not show any changes. These were statistically significant, as displayed in the above tables, and this has not been reported earlier in the literature.

Although the reason why phenylephrine was inert on the arteriolar and capillary systems in the macula can be explained, the inability of tropicamide to exert its action on the ACh receptors in the macular region remains unexplained. As described earlier, this neurotransmitter is responsible for the activity of the circumferential processes of contractile pericytes in constricting capillary lumen whereas the longitudinal processes could affect blood flow adversely by altering the rigidity of the vessels. ACh also releases nitric oxide from the endothelial cells to act upon the smooth muscles, thus relaxing the arteriolar vascular tone [13, 17]. Endothelium also releases endothelin-1, which inhibits NO production. In diabetes, it seems plausible that the imbalance between nitric oxide and endothelin-1 can cause impairment in the natural regulation of vascular functions due to endothelial dysfunction.

Various studies, including ours, show that neither pericytes nor arteriolar smooth muscle exert any change in the macular vasculature of normal and diabetic eyes without retinopathy after instilling a topical mydriatic mixture. The reason for this is not well explained. More intriguing is our finding on the outcome of dilating drops on the macular vessels of eyes with diabetic retinopathy, where the density and perfusion of vessels showed a statistically significant increase.

Although a conclusive inference is difficult on the observations noticed, a few probabilities can be considered. Significant interruption of the blood retinal barrier exists in diabetes [9] at the vascular endothelium, covered with glial cells and pericytes. Pericytes also assists the endothelium in preserving this barrier function. Its breakdown, as in diabetic patients, can increase the intraretinal concentration of the mydriatic applied. As discussed, phenylephrine cannot exert any activity because this region of interest is devoid of alpha-1 receptors.

Tropicamide can theoretically abort the ACh activity in the pericytes, thus limiting its contracting ability and keeping the vascular wall relatively dilated. It seems likely that this parasympatholytic expression of tropicamide in the retina with retinopathy is because of the increased availability of the drug through a weakened blood retinal barrier, blocking the ACh receptors. Hence, no such changes are noticed in the density or perfusion of vessels before the administration of the drug. This insufficient contraction, along with the loss of pericytes, may impede the resting tone of capillaries and make them relaxed and thus attaining a relatively dilated state, is a considerable contribution for increased perfusion [18].

Loss of pericytes also leads to endothelial cell proliferation [19]. ACh acts on this proliferated endothelium to release nitric oxide, which is a potent vasodilator. Contrary to this, endothelium also secretes endothelin-1, an endogenous vasoconstricting peptide. The likely imbalance between NO and endothelin-1 stemming from an altered endothelial dysfunction may also account for the changes observed in the macular capillaries and arterioles of diabetics.

An increase in perfusion in the arterioles can cause passive dilation of downstream vessels. This phenomenon, known as the Windkessel effect, is observed to dampen the fluctuation in blood pressure. This principle cannot be applied in the macular vasculature because the walls of these arterioles contain only minimal elastic tissue on which the Windkassel effect may have only a negligible contribution.

In this study, we used a dilating drug with chlorbutol as a preservative. This preservative is known to weaken the contractile responses of vascular smooth muscles [20]. This could also be an added factor in increasing the perfusion of macular vessels with a defective blood retinal barrier, as noted earlier. Further exploration is required to evaluate the effect of this preservative in retinal vessels.

Flicker-evoked dilatation of vessels and RBC flux is a known phenomenon in retinal vessels. Because the principle of OCT is based on a broad-band light source, a flicker-induced over-response in the anatomically and functionally compromised retinal vessels may also be considered as the cause of our observation. However, this needs further supplementation.

Conclusive note

OCT and OCTA are very commonly employed standard investigative procedures in diabetic and retinal clinics. Based on our findings, we suggest that these tests are done on undilated eyes for a better delineation of macular vasculature if an underlying pathology is present.

Disclosure
Conflict of interests: none declared
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