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Authors Nenad Petrovic*†, Dusan Todorovic*†, Suncica Sreckovic*†, Tatjana Sarenac Vulovic*†, Svetlana Jovanovic*†, Svetlana Paunovic*, Dejan Vulovic‡§, Danijela Randjelovic||, Vojnosanitetski pregled (2020); Online First January, 2021.

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*Clinic of Ophthalmology, Clinical Centre Kragujevac, Kragujevac, Serbia
†Department of Ophthalmology, Faculty of medical sciences, University of Kragujevac, Serbia
‡Center for Plastic Surgery, Clinical Centre Kragujevac, Kragujevac, Serbia
§ Department of Surgery, Faculty of medical sciences, University of Kragujevac, Serbia
‖Aero Medical Institute, Clinic of Ophthalmology, Zemun, Serbia

Correspondence to:
Dusan Todorovic, MD
Clinic of Ophthalmology, Clinical Centre Kragujevac, Kragujevac, Serbia
Zmaj Jovina 30 Street, 34000 Kragujevac, Serbia
Phone: +381 63 1750514 Fax: +381 34 370073
e-mail: drdusantodorovic@yahoo.com
ABSTRACT

Background / Aim. To investigate the impact of diabetic macular ischemia (DMI) on visual acuity (VA) through the analysis of perifoveal capillary network in various stages of diabetic retinopathy (Non Proliferative Diabetic Retinopathy-NPDR and Proliferative Diabetic Retinopathy-PDR). Methods. Qualitative and quantitative analysis of 143 angiograms of patients with different stages of diabetic retinopathy was performed. The degree of macular ischemia was assessed by the analysis of 2 parameters: perifoveal capillary ring i.e. Foveal avascular zone (FAZ) outline irregularity and capillary loss. Finally, a comparison was made between the degree of macular ischemia with the best corrected visual acuity, depending on macular thickness. Results. In the eyes with mild and moderate NPDR, without significant macular thickening, no statistically significant decrease of visual acuity, caused by macular ischemia, was noticed (p=0.81). Opposite, in subgroup with severe NPDR and PDR, without significant macular thickening, statistically significant difference was presented among eyes with moderate and severe macular ischemia comparing to eyes with lower grades of macular ischemia (p=0.021, p=0.018). In eyes with moderate NPDR and mild macular ischemia, the increase in macular thickness resulted in a statistically insignificant decrease in visual acuity compared to eyes with normal macular thickness (p=0.088). But in eyes with severe NPDR, any pathological increase in macular thickness caused a statistically significant decrease in visual acuity, regardless of the degree of macular ischemia (p=0.018-0.040). A similar relationship was also found in eyes with PDR (p=0.017-0.042). In eyes with statistically significant decrease of visual acuity, the most of the examined eyes (98%) had FAZ outline irregularity in nasal perifoveal subfield. Conclusion. In the absence of significant macular thickening, destruction of one-half of the perifoveal capillary network or greater is associated with reduced VA. The location of macular ischemic changes in the nasal parts of the perifoveal capillary ring plays a crucial role in its effects on visual function.

Key words: diabetic retinopathy, macular ischemia, perifoveal capillary network, visual acuity, fluorescein angiography.
Apstrakt

Uvod / Cilj. Ispitati uticaj dijabeteske makularne ishemije (DMI) na vidnu oštrinu analizom perifovealne kapilarne mreže u različitim fazama dijabeteske retinopatije (Neproliferativna dijabeteska retinopatija-NPDR i Proliferativna dijabeteska retinopatija-PDR). Metode. Izvršena je kvalitativna i kvantitativna analiza 143 angiograma pacijenata sa različitim stadijumima dijabeteske retinopatije. Stepen makularne ishemije procenjivan je analizom 2 parametara: perifovealnog kapilarnog prstena tj. nepravilnostima oboda fovealne avaskularne zone (FAZ) i stepena kapilarnog gubitka. Na kraju je izvršeno poredenje između stepena makularne ishemije sa najbolje korigovanom vidnom oštrinom, u zavisnosti od makularne debljine. Rezultati. Kod očiju sa blagom i umerenom NPDR i bez značajnog zadebljanja makule, nije uočen statistički značajan pad vidne oštrine izazvan makularnom ishemijom (p = 0,81). Nasuprot tome, kod očiju sa ozbiljnom NPDR i PDR, bez značajnog zadebljanja makule, utvrđena je statistički značajna razlika u vidnoj oštrini kod očiju sa umerenom i ozbiljnom makularnom ishemijom u poredenju sa očima gde je makularne ishemije bila manjeg stepena (p = 0,021, p = 0,018). Kod očiju sa ozbiljnom NPDR i blagom makularnom ishemijom, povećanje debljine makule rezultiralo je statistički neznačajnim smanjenjem oštrine vida u poredenju sa očima sa normalnom debljinom makule (p= 0,088). Ali kod očiju sa ozbiljnom NPDR, svako patološko povećanje debljine makule izazivalo je statistički značajno smanjenje vidne oštrine, bez obzira na stepen makularne ishemije (p = 0,018-0,040). Slična povezanost je takođe pronadena kod očiju sa PDR (r=0,017-0,042). Kod očiju sa statistički značajnim smanjenjem vidne oštrine, većina njih (98%) je imala iregularnost FAZ konture u nazalnom perifovealnom subpolju. Zaključak. U odsustvu značajnog zadebljanja makule, destrukcija polovine oboda perifovealne kapilarne mreže ili više povezana je sa smanjenim vidne oštrine. Lokalizacija makularnih ishemijiskih promena u nazalnim delovima perifovealnog kapilarnog prstena igra presudnu ulogu u njihovom efektu na vidnu funkciju.

Ključne reči:
dijabeteska retinopatija, makularna ishemija, perifovealna kapilarna mreža, vidna oštrina, fluoresceinska angiografija.
**Introduction**

Diabetic Retinopathy (DR) is the leading cause of vision loss in working active adults. Diabetic macular edema (DME) is defined as thickening of the macula that occurs due to abnormal accumulation of edematous fluid in the retinal tissue. This progressively changes the anatomy of the macula and leads to progressive irreversible photoreceptor degradation and vision loss. The degree of macular thickening is significantly correlated with visual acuity. Diabetic macular edema represents the most common cause of vision loss in patients affected by diabetes mellitus especially in type 2 diabetes\(^1\). The Early Treatment Diabetic Retinopathy Study defined "clinically significant macular edema" and this definition was introduced to indicate the involvement of the center of the macula and its relationship to visual loss\(^2\).

The macula has one of highest metabolic intensity per gram of tissue in the body\(^3\). The outer retinal layers are completely avascular and are dependent on metabolic support by diffusion from the choroidal vascular beds. The inner retina is predominantly supplied by the retinal circulation. The histologic findings have identified three different retinal capillary plexuses in the macular area: the superficial, the deep and the intermediate capillary plexuses. The vessels in the nerve fiber layer and the ganglion cell layer form the superficial capillary plexus (SCP), while the inner and outer plexiform layers receive blood from the deep capillary plexus (DCP) located in the junction between them\(^4,5\).

The very center of the macula, the foveola, is mostly avascular and corresponds approximately to the foveal avascular zone (FAZ) which represents the capillary-free zone. The avascular region of FAZ is surrounded by terminal capillaries forming a perifoveal capillary ring that often has an oval shape with a mean diameter of 362.3± 49.7 μm vertically and 410.8± 80.7 μm horizontally\(^4\).

The size of the FAZ has been intensively studied both in the healthy eyes as well in many retinal disorders. Many studies have shown that the size of the FAZ in normal human eyes can be very variable. In healthy eyes there are large individual variations in the size of FAZ ranging between 0.05 and up to 1.98 mm\(^2\)\(^6,7,8\). Therefore, the correlation between the size of FAZ and visual acuity (VA) in the normal human eye has not been fully established yet. In healthy eyes, the size of the FAZ does not seem to influence visual function\(^9\).
Macular edema is frequently associated with relative ischemia. Diabetic macular ischemia (DMI) is characterized by the occlusion and loss of the macular capillary network. The health and integrity of the capillaries are essential for ganglion cell survival. The persistent ischemia of both the superficial and deep macular capillary network may evolve into permanent neurosensory damage.

Clinically, macular ischemia is recognized by two characteristics: an enlargement or irregularity of the foveal avascular zone and widening of intercapillary spaces in the perifoveal area due to the capillary dropouts. IM can occur with or without macular edema, but it is very rare to find an isolated case of DMI.

Many studies have observed increasing FAZ area in eyes with diabetic retinopathy. Some studies have reported that the relationship between FAZ size and DMI severity occurs from the earliest stages of diabetic retinopathy (NPDR), while others have observed this relationship only in more advanced disease. It is shown that the rate of FAZ enlargement ranged between 5% and 10% of baseline FAZ area per year in eyes with diabetic macular ischemia.

The relationship between FAZ size and visual acuity in retinal diseases remains a matter of discussion. The effects of DMI on visual function are ill defined. Some patients maintain visual acuity near to normal levels in the presence of profound ischemia. Evidence of enlargement of the foveal avascular zone greater than 1,000 μm generally indicates visual loss.

Historically, since its introduction in the 1960s, conventional Fluorescein Angiography (FA) is the gold standard procedure for evaluating the degree of DMI in patients with DR. This technique typically shows enlargement and irregular shape of FAZ, interruptions of the perifoveal capillary ring, and large areas of retinal hypofluorescence due to the absence of macular capillaries.

While previous studies have focused mainly on investigating changes in the size and shape of FAZ in ischemic maculopathy, this paper primarily analyzes changes in the perifoveal capillary ring to determine whether its alterations may be a good indicator of the ischemic process.
Methods
The study was conducted at the Clinic of ophthalmology, Clinical center Kragujevac, Serbia. It was designed as retrospective, cross sectional study. We performed a qualitative and quantitative analysis of 143 angiograms of patients with different stages of diabetic retinopathy. In these patients, the diagnostic procedure of fluorescein angiography was performed in the period from 2008 to 2019. The study included 123 patients: angiograms of only one eye were analyzed in 123 patients and angiograms of both eyes in 20 patients.

The main inclusion criterion was the existence of DR. Patients with cataract, with high refractive error, corneal leucoma, vitreal haemorrhage, glaucoma, uveitis, previous ocular surgery or trauma, tractional retinal deatachment, were not able to participate in the study. Those who received anti VEGF therapy or intravitreal steroids were also excluded.

All angiograms were obtained by performing a standard fluorescein angiography procedure using a digital retinal camera (Carl Zeiss, Meditec, Inc., Dublin, CA) and an intravenous infusion of 5-14 ml of 10% sodium fluorescein. For each angiogram analyzed, there were accompanying Fundus color photographs as well as the data on visual acuity, intraocular pressure and biomicroscopic status of ocular media.

For all analyzed angiograms, there was an accompanying OCT image (Stratus Optical Coherence Tomography - OCT3, Carl Zeiss Meditec, Inc., Dublin, CA) with data of mean foveal thickness. For all the participants the best corrected visual acuity was measured by using Snellen chart.

All these data were obtained from the file and electronic database archived in the Department of medical retina at the Clinic of ophthalmology, Clinical center Kragujevac.

Initially, the central parts of the angiogram of 3x3 mm were excised, and then they were magnified five times. The angiograms processed in this way corresponded to the area of five macular fields according to the ETDRS grid cells scheme: a central foveal ring with 1mm diameter and an inner macular ring (pericentral) with 3mm diameter divided in four subfields (nasal, temporal, superior, and inferior) 12. FA angiograms were then independently evaluated by the two experienced retinal specialists.

The classification of Diabetic Retinopathy (DR) was performed according to ETDRS grading system 12. According to these criteria, DR was classified into two basic stages: Non Proliferative Diabetic Retinopathy, and Proliferative Diabetic Retinopathy (PDR). NPDR is further divided into mild, moderate and severe.
The evaluation of 3 parameters was performed on the central parts of the angiogram: FAZ outline i.e perifoveal capillary ring, capillary loss and intensity of fluorescein leakage. The early-phase angiograms (up to 20 seconds) were used to observe the superficial capillary plexus, while late-phase angiograms were used to assess leakage intensity i.e BRB status.

In each of the 4 analyzed subfield (nasal, superior, temporal and inferior), the irregularity of the perifoveal capillary ring was assessed as follows: Grade 0, normal (no disruption of the FAZ in that subfield); Grade 1, questionable (discrete ring irregularities in that subfield, but the changes are not clearly pathological); Grade 2, mild (outline of the FAZ is destroyed to 25% in that subfield); Grade 3, moderate (outline of the FAZ is destroyed 25% to 50% in that subfield); Grade 4, severe (capillary outline of the FAZ is completely destroyed in that subfield).

The cumulative FAZ outline irregularity was classified as follows: Grade 0, normal (no disruption of the FAZ); Grade 1, questionable (outline not smoothly round or oval, appreciable irregularities seen, but changes are not clearly pathologic); Grade 2, mild (outline of the FAZ is destroyed for less than half the original circumference <180°); Grade 3, moderate (outline of the FAZ is destroyed for greater than half the original circumference >180°); Grade 4, severe (capillary outline of the FAZ is completely destroyed).

Outline of FAZ was considered normal when the grade ranged from 0 to 1, suspiciously abnormal when the grade was 2 and abnormal when the grade ranged from 3 to 4.

In each of the 4 analyzed subfields (nasal, superior, temporal and inferior), the capillary loss was assessed as follows: Grade 0, absent, no loss; Grade 1, questionable; Grade 2, minimal (up to 25% loss in the subfield); Grade 3, moderate (>25% and up to 50% loss in the subfield); Grade 4, severe (>50% loss in the subfield).

The cumulative capillary loss for all four subfields was graded according to the scale: Grade 0, absent, no loss; Grade 1, questionable; Grade 2, minimal (loss up to 25% of the entire perifoveal capillary network); Grade 3, moderate (>25% and up to 50% loss of the entire perifoveal capillary network); Grade 4, severe (>50% loss of the entire perifoveal capillary network).

Capillary loss was considered normal when the grade ranged from 0 to 1, suspiciously abnormal when the grade was 2 and abnormal when the grade ranged from 3 to 4.
Using the fluorescence of the perifoveal vessels as comparison, intensity of leakage was classified into 4 grades: Grade 0 corresponded to the absence of leakage; Grade 1 corresponded to presence of low-intensity leakage (less fluorescent than vessels); Grade 2 corresponded to presence of midintensity leakage (similar fluorescence to the vessels); Grade 3 to presence of high-intensity leakage (more fluorescent than the vessels); Grade 4, intensive early diffuse dye leakage that completely blocks the observation of individual blood vessels.

Finally, according to the analyzed parameters in all four subfields, a cumulative diabetic macular ischemia was calculated and classified as none (Grade 0), questionable (Grade 1), mild (Grade 2), moderate (Grade 3) and severe (Grade 4). Grades 0 and 1 were considered normal, grade 2 was suspected to be pathological, and grades 3 and 4 were considered pathological.

As a pathological status of increased macular thickness the OCT 3 definition was used $\geq 305 \, \mu m$ for males, $\geq 290 \, \mu m$ for females. We compared a cumulative diabetic macular ischemia with the best corrected visual acuity depending to the macular thickness.

In analyzing statistical date SPSS version 22 (IBM Corp., Armonk, NY, USA) was used. Examination of the incidence of FAZ outline irregularity, capillary loss and dye leakage, was done by using Chi-square test and ANOVA. The value of $p$ lower than 0.05 was considered to be statistically significant.

**Results**

The mean age of the participants was $64.27 \pm 7.3$ years (range 48 - 72 years). Male to female ratio was equal (male 75, female 68). No statistical significant difference was noticed, $p=0.069$. The mean duration of diabetes mellitus was $15.12 \pm 6.8$ years. Diabetes mellitus type I was presented in 37 patients, while the other 86 patients had DM type 2. As it is shown in Table 1, 120 eyes had NPDR (42 eyes mild, 41 eyes moderate and 37 eyes severe NPDR) while 23 eyes had proliferative diabetic retinopathy. Until the moment of FA, 67 eyes had previous focal laserphotocoagulation, while in 38 eyes (23 eyes with PDR and 15 eyes with NPDR) the panretinal laserphotocoagulation was done. Until the moment of FA none of the eyes had received intravitreal anti-VEGF therapy. The Table 1 shows the distribution of three parameters according to the gradation, as well as the 4 subfields of the perifovea.
The cumulative DMI compared with the best corrected visual acuity, depending on the macular thickness, was shown in Table 2. In the eyes with mild and moderate NPDR none of the eyes had cumulative DMI grade 3 and 4. In the eyes with severe NPDR moderate and severe (Grade 3 and 4) macular ischemia was measured in 6 (16.2%) eyes, while in the eyes with PDR moderate and severe macular ischemia was presented in 12 (52.2%) eyes. According to the grade of ischemia, analyzing the eyes with mild and severe NPDR a statistically significant difference was noticed (p=0.018). Comparing severe with moderate NPDR statistical significance was measured as well (p=0.037). In the eyes with PDR, the highest statistically significant difference was comparing them with the mild (p=0.002), then with the moderate (p=0.022), and finally with the severe NPDR (p=0.041).

Figures 1a and 1b show FAZ outline damaged ≤ 180° of the original circumference.

Figures 2a and 2b show FAZ outline damaged ≥ 180° of the original circumference with capillary loss ≤ 50%.

In subgroups with mild and moderate NPDR, without significant macular thickening, no statistically significant decrease of visual acuity, caused by macular ischemia, was noticed (p=0.81). Opposite, in subgroup with severe NPDR, and without significant macular thickening, statistically significant difference was presented among eyes with moderate and severe macular ischemia (Grade 3 and 4), comparing to the eyes with lower grades of macular ischemia (p=0.021). The similar finding was found in the eyes with PDR (p=0.018).

In the eyes with statistically significant decrease of visual acuity, the most of the examined eyes (98%) had FAZ outline destruction in nasal subfield, while superior and inferior subfield was destructed in 71%, and temporal subfield 68% of the examined eyes.

As shown in Figures 3a and 3b, the FAZ outline damaged in the nasal subfield leads to a significant reduction in visual acuity.

In the eyes with the mild NPDR, and without macular ischemia, the increased macular thickness caused a statistically insignificant decrease in visual acuity compared to the eyes with normal macular thickness (p=0.072). The similar relationship was found in the eyes with the moderate NPDR (p=0.051). In the eyes with the moderate NPDR and mild macular ischemia, the increase in macular thickness resulted in a statistically insignificant decrease in visual acuity compared to the eyes with the normal macular thickness (p=0.088). But in the eyes with the severe NPDR, any pathological increase in macular
thickness caused a statistically significant decrease in visual acuity, regardless of the degree of macular ischemia (p=0.023, p=0.021, p=0.018, p=0.040, p=0.038). The similar relationship was found in the eyes with PDR (p=0.023, p=0.017, p=0.042).

**Discussion**

The macula is a unique structural and functional region of the retina and its nutrition must be well balanced. The outer retinal layers are completely avascular and are dependent on the metabolic support by the diffusion from the choroidal vascular beds. The inner retina is predominantly supplied by the retinal circulation. The parafoveal region of the macula is supplied by the dense vasculature with approximately 9 pairs of arterioles and venules. The histologic findings have identified three different retinal capillary plexuses in the macula area: the superficial, the deep, and the intermediate capillary plexuses. The vessels in the nerve fiber layer and the ganglion cell layer form the superficial capillary plexus (SCP), while the inner and outer plexiform layers receive blood from the deep capillary plexus (DCP) located in the junction between them. At the level of the SCP, mean vascular density is 0.28 ± 0.1 mm², while at the level of the DCP, mean vascular density is 0.37 ± 0.12 mm². The very center of the macula, the foveola, is completely avascular and corresponds approximately to the foveal avascular zone. The size of the FAZ has been intensively studied both in the healthy eyes as well in many retinal disorders. Many studies have shown that in healthy eyes there are large individual variations in the size of FAZ ranging between 0.05 and up to 1.98 mm². A correlation between FAZ size and visual acuity in the normal human eyes has not yet been precisely determined. In the healthy eyes, the size of the FAZ does not seem to influence visual function. Nevertheless, the relationship between FAZ size and visual acuity in retinal vascular diseases remains a matter of discussion.

DME represents the most common cause of vision loss in patients affected by diabetes mellitus. The degree of macular thickening is significantly correlated with visual acuity. The common pathway that results in DME is disruption of the inner blood retinal barrier. Macular edema is frequently associated with relative ischemia. Diabetic macular ischemia is characterized by the occlusion and loss of the macular capillary network. The capillary
dropout may result in larger areas of nonperfusion with widening of intercapillary spaces in the perifoveal area. Diabetic macular ischemia is an important clinical feature of diabetic retinopathy. Clinically, DMI is defined by an enlargement of the foveal avascular zone and paramacular areas of capillary nonperfusion. The FAZ seems to get larger as the stage of retinopathy advances.

DMI can occur with or without macular edema, although it is very rare to find an isolated case of DMI. Thus, each macular edema is the result of two inter-related pathophysiological mechanisms that occur simultaneously: capillary occlusions and disruption of the blood retinal barrier. Even in the absence of macular edema in diabetic eyes, abnormalities of the FAZ are often seen, and they include irregular margins and widening of the intercapillary spaces. FA typically shows the large areas of retinal hypofluorescence due to the absence of macular capillaries. In the case of macular ischemia, early-phase FA usually can demonstrate enlargement of FAZ, irregularity of FAZ outline, a broken foveal capillary ring and widening of perifoveal capillary spaces. Also, based on the extent of dye leakage, the FA provides information on the condition of the inner blood retinal barrier. However, fluorescein leakage does not always correlate with retinal thickness; a simple diffusion of fluorescein without retinal thickening is not included as part of the definition of macular edema.

Optic coherence tomography is another useful clinical tool that can be used for the detection of DMI. The ischemic areas of macula appear thin during OCT investigation. However, the presence of edema usually make the results of OCT difficult to interpret.

Many studies have observed increasing FAZ area in eyes with diabetic retinopathy. Some studies have reported that the relationship between FAZ size and DMI severity occurs from the earliest stages of diabetic retinopathy, while others have observed this relationship only in more advanced disease. This discrepancy is most likely due to the large intersubject variability of the FAZ.

In our study, we have shown that some degree of macular ischemia may exist in the earliest stages of diabetic retinopathy (mild and moderate NPDR) but the macular ischemia progressively intensifies during the advanced stages of the disease. There is a statistically significant difference in the degree of macular ischemia between the severe NPDR in relation to the mild NPDR (p=0.0016) and the moderate NPDR (p=0.0022). This
difference is even more pronounced between PDR and the mild NPDR (p=0.0011) and the moderate NPDR (p=0.0014). Also, the degree of macular ischemia is statistically slightly higher in PDR compared to the severe NPDR (p=0.041). This finding is consistent with previous studies that have shown that in DR the FAZ has been enlarged and seems to get larger as the stage of retinopathy advances \(^{45}\). It is estimated that the rate of FAZ enlargement was between 5% and 10% of baseline FAZ area per year in the eyes with diabetic macular ischemia \(^{18}\).

In this paper, the FAZ outline irregularity has been demonstrated to be a good indicator of macular ischemia. The parameters related to the shape of the FAZ may be better parameters for monitoring the FAZ than its size. This is in agreement with the results of previous studies that have shown that the circularity and axial ratio are changed significantly more in the eyes with diabetic retinopathy than the size of the FAZ \(^{46}\).

The effects of DMI on visual function are poorly defined. Some patients may have an almost normal level of visual acuity in the presence of profound ischemia. Despite this, numerous studies have demonstrated the link between the presence of DMI and the loss of visual function \(^{19,47,48}\). Some patients can experience sudden and severe decreases in visual acuity and in these cases DMI is often responsible for unexplained visual loss, even if the clinical stage of the disease is early or mild \(^{49}\).

Previous studies have mainly focused on the relationship between the increase in FAZ size in DR and its effect on visual acuity. It is generally accepted that doubling of the FAZ size indicates ischemic maculopathy. The enlargement of the foveal avascular zone greater than 1,000 μm generally indicates visual loss \(^{19,50,51,52}\). In their study, Arend et al showed that in diabetics with decreased visual acuity (0.5 or worse), FAZ was enlarged by 73% compared with patients whose visual acuity was normal or near to normal (median VA 0.8) \(^{47}\).

Due to large variability in FAZ size and topology in both normal and diseased eyes, we were mainly focused on determining FAZ outline irregularities and their effect on visual acuity. In our work, in the eyes with the mild and the moderate NPDR, without significant macular thickening, macular ischemia does not affect visual function (p=0.068, p=0.059). Our study demonstrated that visual function was affected only in those with the moderate to the severe macular ischemia.

In eyes with severe NPDR and no significant macular thickening, there was a statistically significant difference in visual acuity (p=0.033) between eyes with FAZ outline destruction.
greater than half the original circumference > 180 ° (Grade 3 and 4) compared to eyes where these alterations are milder (grade 1 and 2). A similar finding was found in eyes with PDR (p=0.025).

In the eyes with the severe NPDR and PDR, in the absence of significant macular thickening, only the destruction of the FAZ outline for greater than half of the original circumference >180 ° (grade 3 and 4) results in a significant decrease in visual acuity. Our results confirm, therefore, a definite link between macular ischemia and visual function. Our findings indicate that the location of macular ischemic changes plays a critical role in its effects on visual function. In our work, the ischemia of the nasal parts of the parafoveal capillary plexus had particularly strong impact on VA. In almost all eyes with capillary non-perfusion in this part of the FAZ outline, there was a decrease in visual acuity. The capillary network in the nasal parafoveal parts supplies the papillomacular nerve fibers, originating from the fovea. We supposed that ischemia in these locations, which contain a high density of axons originating from the macula, may have an association with reduction in VA. This finding is consistent with the results of other studies that observed a strong significant association between papillomacular ischemia and VA, independent of the FAZ size 49,53.

The relationship of edema to changes in visual function is complex. In the eyes with the mild NPDR and without macular ischemia, the increased macular thickness caused a statistically insignificant decrease in visual acuity compared to the eyes with normal macular thickness (p=0.072). The similar relationship was also found in the eyes with the moderate NPDR (p=0.051). In the eyes with the moderate NPDR and the mild macular ischemia, the increase in macular thickness resulted in a statistically insignificant decrease in visual acuity compared to the eyes with the normal macular thickness (p=0.088). As it is shown in Table 2, in eyes with severe NPDR, any pathological increase in macular thickness caused a statistically significant decrease in visual acuity, regardless of the degree of macular ischemia. The similar relationship was also found in the eyes with PDR.

Our results suggest that ischemic maculopathy may be compatible with good visual acuity if not accompanied by edema. Occurrence of macular edema caused by leakage from residual macular capillaries leads to a greater decrease in visual acuity which is in agreement with the findings of other studies 14,19. As mentioned earlier, the fluorescein leakage does not always correlate with retinal thickness. However, in our study, there was a
significant agreement among the degree of dye leakage and increased macular thickness in approximately 75% of the eyes.

DMI causes severe irreversible vision loss and the severity of the disease increases with time\textsuperscript{16,17}. DMI is associated with a poor prognosis of diabetic retinopathy. Some studies have linked DMI as a risk factor for progression of diabetic retinopathy severity\textsuperscript{54}. The one-year risk of patients with DMI to develop progressive diabetic retinopathy was found to be almost 42%, while the diabetics without DMI have significantly lower risk for disease progression of 18%\textsuperscript{55}.

Until now, there is no defined successful treatment method for DMI. The only possible treatment seems to be the management of the risk factors. These include the control of blood sugar levels and optimum blood pressure control. In addition, other risk factors like anemia and nephropathy should also be controlled\textsuperscript{56}.

Today, the intravitreal application of anti-VEGF drugs is a generally accepted method of treating macular edema and those drugs can significantly reduce retinal edema. However, several studies have suggested that anti-VEGF therapy could have a potential ischemic effects and further compromise the retinal circulation\textsuperscript{57,58,59}. In this regard, a good assessment of the degree of macular ischemia is necessary before the use of these drugs in the treatment of macular edema.

**Conclusion**

Diabetic macular ischemia is an important clinical feature of diabetic retinopathy and some degree of macular ischemia may exist in the earliest stages of the disease. Results of our study suggest that the assessment of the Foveal avascular zone outline irregularity may be a good indicator of macular ischemia. Ischemic maculopathy may be compatible with good visual acuity if not accompanied by edema. In the absence of significant macular thickening, destruction of one-half of the perifoveal capillary network or larger is associated with reduced visual acuity. Occurrence of macular edema caused by leakage from residual macular capillaries leads to a greater decrease in visual acuity. The location of macular ischemic changes in the nasal parts of the perifoveal capillary ring has a particularly strong impact on visual acuity. Before using anti-VEGF drugs in the treatment of macular edema, a good assessment of the degree of macular ischemia is required due to their potential detrimental effect on the deterioration of macular perfusion.
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**Table 1** – The distribution and gradation of FAZ outline, capillary loss and dye leakage between the groups

| DR      | Grade       | FAZ outline Subfield | Capillary loss Subfield | Dye leakage Subfield |
|---------|-------------|----------------------|--------------------------|----------------------|
|         |             | N | S | T | I | N | S | T | I | N | S | T | I  |
| NPDR    |             | 0 | 38| 40| 41| 40| 38| 39| 40| 39| 36| 37| 38| 37 |
| Mild    |             | 1 | 3 | 1 | 1 | 1 | 3 | 2 | 2 | 2 | 6 | 5 | 4 | 5  |
| n=42    |             | 2 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0  |
| NPDR    |             | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0  |
| Moderate|             | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0  |
|         |             | 0 | 29| 32| 34| 33| 31| 33| 36| 35| 29| 33| 35| 34 |
| NPDR    |             | 1 | 7 | 6 | 6 | 5 | 5 | 5 | 4 | 4 | 10| 8 | 6 | 7  |
| Moderate|             | 2 | 2 | 2 | 1 | 3 | 3 | 3 | 1 | 2 | 2 | 0 | 0 | 0  |
| n=41    |             | 3 | 2 | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0  |
| NPDR    |             | 4 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0  |
| Moderate|             | 0 | 18| 22| 26| 22| 20| 24| 26| 25| 21| 24| 27| 23 |
| Severe  |             | 1 | 6 | 8 | 5 | 7 | 6 | 8 | 9 | 7 | 9 | 9 | 8 | 10 |
| n=37    |             | 2 | 7 | 4 | 3 | 4 | 9 | 4 | 2 | 4 | 5 | 3 | 2 | 3  |
| PDR     |             | 3 | 3 | 2 | 2 | 2 | 2 | 1 | 0 | 1 | 2 | 1 | 0 | 1  |
| n=23    |             | 4 | 3 | 1 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0  |
|         |             | 0 | 2 | 5 | 7 | 4 | 4 | 3 | 4 | 7 | 1 | 2 | 12| 3   |
|         |             | 1 | 2 | 4 | 5 | 4 | 5 | 6 | 4 | 5 | 7 | 10| 5 | 10 |
| PDR     |             | 2 | 7 | 6 | 3 | 8 | 9 | 9 | 13| 8 | 12| 9 | 6 | 9  |
| n=23    |             | 3 | 7 | 5 | 4 | 4 | 3 | 2 | 2 | 2 | 3 | 2 | 0 | 1  |
|         |             | 4 | 5 | 3 | 4 | 3 | 2 | 1 | 0 | 1 | 1 | 0 | 0 | 0  |
DR – diabetic retinopathy, NPDR – nonproliferative diabetic retinopathy, PDR – proliferative diabetic retinopathy, FAZ – foveal avascular zone

**Table 2** – The distribution of cumulative diabetic macular ischemia, mean foveal thickness and the best corrected visual acuity between the groups

| DR   | Grade | Cumulative DMI | Mean foveal thickness / mean BCVA | Statistical significance |
|------|-------|----------------|-----------------------------------|-------------------------|
|      |       |                | <305(290) µm/BVCA                  | >305(290) µm/BVCA       | CA                      |
|      |       |                |                                    |                         |                         |
| NPDR | Mild  | 0              | 39                                 | 0.90                    | 3                       | 0.85                    | p=0.072                 |
|      |       | 1              |                                     |                         |                         |                         |
|      |       | 2              |                                     |                         |                         |                         |
|      |       | 3              |                                     |                         |                         |                         |
|      |       | 4              |                                     |                         |                         |                         |
|      | Modern| 0              | 29                                 | 0.90                    | 6                       | 0.70                    | p=0.051                 |
|      |       | 1              |                                     |                         |                         |                         |
|      |       | 2              |                                     |                         |                         |                         |
|      |       | 3              |                                     |                         |                         |                         |
|      |       | 4              |                                     |                         |                         |                         |
|      | Severe| 0              | 12                                 | 0.70                    | 2                       | 0.35                    | p=0.023*                |
|      |       | 1              |                                     |                         |                         |                         |
|      |       | 2              |                                     |                         |                         |                         |
|      |       | 3              |                                     |                         |                         |                         |
|      |       | 4              |                                     |                         |                         |                         |
|      |       | 0              |                                     |                         |                         |                         |
|      | PDR   | 1              | 7                                  | 0.75                    | 2                       | 0.35                    | p=0.021*                |
|      |       | 2              |                                     |                         |                         |                         |
|      |       | 3              |                                     |                         |                         |                         |
|      |       | 4              |                                     |                         |                         |                         |
|      |       | 0              |                                     |                         |                         |                         |
|      |       | 1              | 2                                  | 0.65                    | 0                       | /                       | /                       |
|      |       | 2              |                                     |                         |                         |                         |
|      |       | 3              |                                     |                         |                         |                         |
|      |       | 4              |                                     |                         |                         |                         |
|      |       | 0              |                                     |                         |                         |                         |
|      |       | 1              | 2                                  | 0.65                    | 0                       | /                       | /                       |
|      |       | 2              |                                     |                         |                         |                         |
|      |       | 3              |                                     |                         |                         |                         |
|      |       | 4              |                                     |                         |                         |                         |

*-statistically significant
DR – diabetic retinopathy, NPDR – nonproliferative diabetic retinopathy, PDR – proliferative diabetic retinopathy, DMI - diabetic macular ischemia, BVCA - the best corrected visual acuity

FIGURES

Fig 1a – enlarged FAZ with FAZ outline ≤ 180°; 1b - magnified 5 times

Fig 1b – damaged

Fig 2a – the cumulative FAZ outline damaged ≥ 180° with capillary loss ≤ 50%; 2b - magnified 5 times
Figure 3a – FAZ outline damaged in nasal subfield; 3b - magnified 5 times)

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