Analysis of foveal avascular zone in different stages of non/proliferative diabetic retinopathy at a tertiary eye care hospital

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ABSTRACT

Background: *To evaluate changes seen in Foveal Avascular Zone (FAZ) on Fundus Fluorescein Angiography in different stages of Non-proliferative Diabetic Retinopathy (NPDR) and its association with systemic conditions like hyperlipidemia, hypertension and nephropathy.*

Methods: *All diabetic patients visiting our MS Ramaiah hospital were screened for diabetic retinopathy from September 2012 to September 2015. The sample size was 30 eyes of 21 patients and duration of study was 2 years.*

Results: *Among 21 patients 80% of the study populations were males. Majority of patients (53%) were in the age group of 51 to 60 years. In our study, poor glycemic control is significantly associated with severe Non-proliferative Diabetic Retinopathy with p<0.001. In severe NPDR 50% patients had grade 2 outline, 20% had grade 3 outline and in moderate NPDR 60% patients had grade 2 outline. Thus, greater incidence of macular ischemia was seen in patients with more advanced forms of NPDR. 16.6% had altered renal profile in our study of which 60% had grade 2 FAZ outline changes and 40% had grade 3 FAZ outline changes. Thus a significant association was found between FAZ outline and nephropathy.*

Conclusion: *Macular ischemia thus appears to be a marker for the severity of diabetic retinal disease and other systemic disorders like nephropathy. As is proven in our study the presence of structural and morphologic changes in the perifoveal circulation correlates significantly with changes in visual function and presence of metabolic disorders like nephropathy. Effective screening of all diabetic patients may aid in early diagnosis of diabetic maculopathy and nephropathy and thereby prevent the associated ocular and systemic morbidity and mortality.*

Keywords: *Diabetic maculopathy, Diabetic nephropathy, Diabetic retinopathy, Foveal Avascular Zone, Fundus Fluorescein Angiography*

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INTRODUCTION

Diabetes Mellitus (DM) is an abnormality of blood glucose metabolism due to altered insulin production or activity. Diabetic Retinopathy (DR) is one of the systemic complications of diabetes mellitus which is characterized by gradually progressive alterations in the retinal microvasculature.[1] It is a major cause of avoidable blindness in adults between 20 to 74 years of age.[1,2] Patients with Diabetic Retinopathy are 25 times more likely to become blind than non-diabetics. Good glycemic control arrests development and progression of Diabetic Retinopathy and decreases the chances of visual loss.[3]

Although a number of factors have been implicated in the development of diabetic retinopathy and subsequent blindness, the overwhelming predictor is the length of time the patient has had diabetes. Moreover, since proliferative retinopathy does tend to occur along with diabetic nephropathy, life expectancy after development of severe retinopathy and blindness is often limited.

Diabetic retinopathy in type 1 diabetes induces vision loss mainly due to the formation of new vessels in the fundus and development of proliferative retinopathy, whereas in type 2 diabetes vision loss is most commonly due to macular edema and proliferative retinopathy is relatively rare.[1] whereas macular ischemia is a relatively uncommon though important cause of visual loss in diabetics because it is not amenable to treatment unlike Proliferative Diabetic Retinopathy (PDR) and Diabetic Mascular Edema (DME).

The Foveal Avascular Zone (FAZ) is an area located in the center of the macula which is physiologically avascular. It is this region that provides highest visual acuity, contrast vision and color vision, with a maximum ratio of photoreceptors (cones) to nerve fibers.[4]

There is a large inter-individual variability of foveal avascular zone size in normal population.[5] The FAZ enlarges in certain vasoocclusive disorders like diabetic retinopathy[5,6], sickle cell disease[7], talc retinopathy.[8] It occurs due to occlusion of perifoveal capillaries or arterioles and tends to get larger as stage of retinopathy advances.[5] Reduced capillary density

leads to enlargement of FAZ and perifoveal intercapillary area.[9]

Assessing the severity of ischemia in diabetic patients could lead to better understanding and identification of ischemic diabetic maculopathy. Severity of perifoveal capillary abnormalities is classified by size and outline of FAZ and extent of foveal capillary loss.[10] Fundus Fluorescein Angiography(FFA) is an important clinical tool in recognition of the vascular changes associated with Diabetic Retinopathy.[11,12] It helps detect the presence of macular ischemia in diabetic retinopathy by observing the characteristics of FAZ like:

- Irregularity of FAZ margins.
- Erosion of capillaries surrounding FAZ.
- Budding into FAZ.
- Widening of inter-capillary spaces.[5]

Although FFA is effective for quantification of early macular capillary changes these changes are not reflected in visual acuity loss until the disease is well advanced.[9] The purpose of this study was to examine the FAZ on FFA in diabetic population with diagnosis of non-proliferative diabetic retinopathy for any signs of macular ischemia based on criteria laid down by Bresnick et al[5] in order to firstly confirm advancing FAZ abnormalities with stage of diabetic retinopathy and its impact on best corrected visual acuity, secondly to study the co-relation between macular ischemia and selected systemic diseases like hyperlipidemia, hypertension and nephropathy.

AIMS

To evaluate changes seen in foveal avascular zone ie foveal avascular zone maximum diameter and outline on fundus fluorescein angiography in different stages of non-proliferative diabetic retinopathy (NPDR) and its association with systemic conditions like hyperlipidemia, hypertension and nephropathy.

MATERIALS AND METHODS

Source of data: Patients attending the Retina Clinic of M S Ramaiah medical college, Eye department from September 2012 to September 2015.

Method of Data collection

***Study Design*:** Hospital based prospective observational study.

***Sample Size*:** 30 eyes of 21 patients.

***Duration of study*:** 2 years.

Inclusion Criteria: All patients diagnosed clinically as non-proliferative diabetic retinopathy and willing to undergo the diagnostic imaging in the form of FFA.

Exclusion Criteria

- Any macular pathology precluding the view of foveal avascular zone like macular scars.
- Concomitant fundus pathology that could potentially affect foveal avascular zone like arteriovenous occlusions, uveitis etc.
- Dense media opacities (corneal opacities, dense cataract, vitreous hemorrhage) that preclude obtaining images of adequate quality.
- Patients in whom Fundus Fluorescein Angiography was contraindicated due to co-existing systemic disorders or allergy to Fluorescein dye.
- Patients who have undergone any prior photocoagulation in macular region.

Collection of data

A detailed history was obtained from all patients. Examination included visual acuity assessment by Snellen's chart, refraction & best corrected visual acuity. Anterior segment examination was performed by Slit lamp biomicroscopy. Fundus examination was performed with an indirect ophthalmoscope and slit lamp biomicroscopy with a 78 D lens. All patients enrolled in the study underwent a Lipid Profile analysis, Renal Function Testing and Serum HbA_1C level estimation. Fasting total plasma cholesterol >200mg/dl**,** Blood Urea >40mg/dl**,** Serum Creatinine >1.5 mg/dl and Urine albumin 1+ were considered abnormal. Glycemic control was categorized according to the Glycosylated Haemoglobin (HbA1C) levels as excellent (<6%), good (6-8%), fair (8-10%) and poor (above 10%).

All the patients diagnosed with non-proliferative diabetic retinopathy underwent Fundus Fluorescein Angiography (FFA) using 3ml of 20% sodium fluorescein dye after obtaining written informed consent.

NPDR was classified as mild, moderate and severe according to the ETDRS. criteria.[15]

Fundus Fluorescein Angiography was performed using the Canon digital camera.

A "peak phase" photograph of the central 35 degrees centered on the fovea was taken in all cases for FAZ analysis. The greatest diameter and area of the FAZ was measured using the software tool available on the FFA imaging system.

The peak phase pictures were also analysed for FAZ irregularities based on criteria laid down by Bresnick[5] in the FAZ like:

- Irregularity of FAZ margins.
- Erosion of capillaries surrounding FAZ.
- Budding into FAZ
- Widening of inter-capillary spaces.

Morphological changes in the FAZ were assessed by grading the FAZ diameter and FAZ outline into three grades.

FAZ Diameter:
Grade 1: <350 mm
Grade 2: 350 to 750 mm
Grade 3: >750 mm

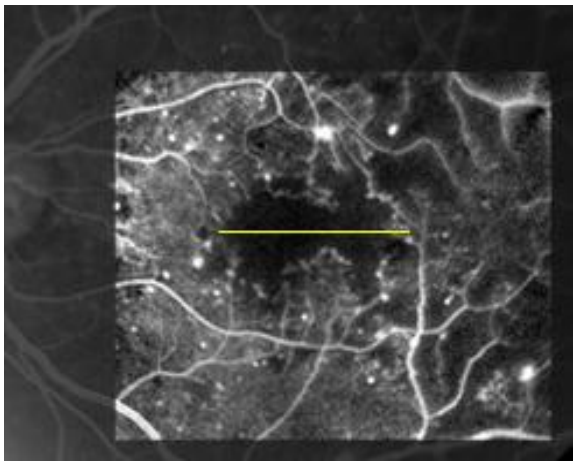


Fig. 1

FAZ Outline:
Grade 1: Normal perifoveal architecture.
Grade 2: Perifoveal capillary network destroyed <1/2 circumference.
Grade 3: Perifoveal capillary network destroyed >1/2 circumference

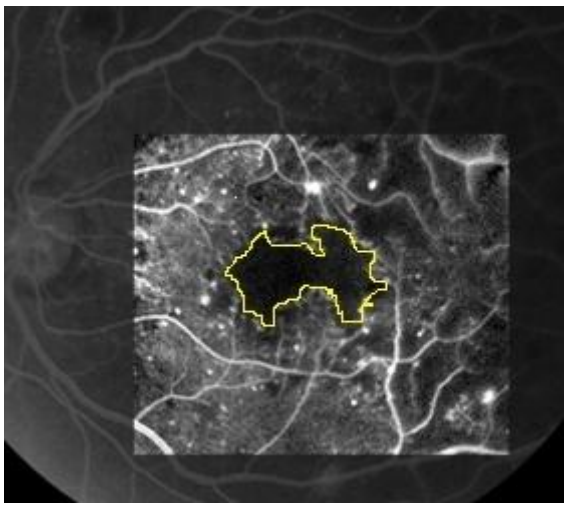


Fig. 2

Statistical Methods: Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients Chi-square/2x3, 3x3, 4x3 Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Significant figures
+ Suggestive significance (p value: 0.05<p<0.10)
* Moderately significant (p value: 0.01<p≤ 0.05)
** Strongly significant (p value: p≤0.01)

RESULTS

Study design: A prospective clinical study consisting of 30 eyes of 21 patients was undertaken at MS Ramaiah hospital eye department to analyze the foveal avascular zone changes in different stages of NPDR (10 eyes in each group of mild, moderate and severe NPDR) in absence of macular edema using IV FFA.

Majority of patients (53%) were in the age group of 51 to 60 years. The mean age of patients in our study was 58.7±2.33 years. 80% of the study populations were males.

Table 1: Type of DM in different stages of NPDR

Type of DM	NPDR		
	Mild	Moderate	Severe
Type I	0	3(30.0%)	2(20.0%)
Type II	10(100.0%)	7(70.0%)	8(80.0%)
Total	10	10	10

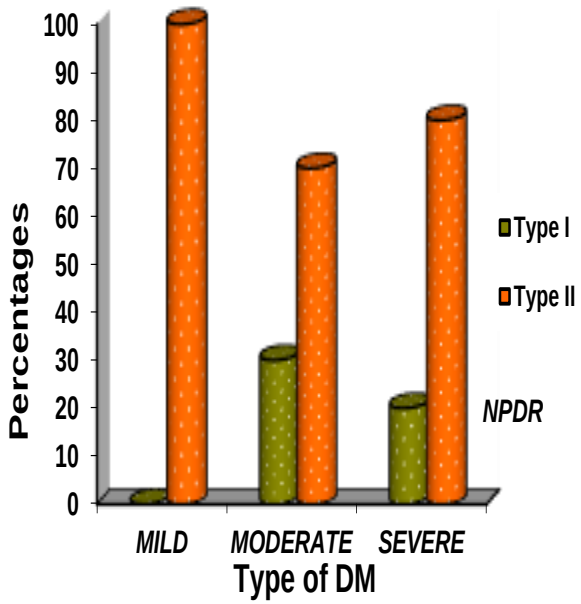


Fig. 3

100% of patients with mild NPDR had type 2 DM, 70% patients with moderate NPDR had type 2 DM and 80%

of patients with severe NPDR had type 2 DM. Distribution of type of DM was not statistically significant(p=0.32) across the various stages of NPDR . 60% of moderate and 60% of severe NPDR had more than 10 years duration of DM in our study which was statistically significant with a p value of 0.005. In our study, 40% of patients with severe NPDR had BCVA <6/18 which was statistically significant. All eyes with mild and moderate NPDR had BCVA better than 6/12. In our study, poor glycemic control is significantly associated with severe NPDR with p<0.001. 80% of severe NPDR, 60% of mild and 40% of moderate NPDR patients had associated hypertension which was not statistically significant (p<0.248) across the three stages of NPDR. Regarding lipid profile, 40% of patients with moderate NPDR had altered lipid profile, which was statistically significant (p=0.023). Correlating renal profile in different stages of NPDR, 20% of moderate and 30% of severe NPDR had altered renal profile, but were not statistically significant (p=0.321).

Table 2: FAZ dimensions in different stages of NPDR

FAZ dimensions	NPDR			p value
	Mild	Moderate	Severe	
Area in sqmm	0.36±0.12	0.74±0.30	1.33±0.39	<0.001**
Diameter in mm	0.64±0.06	1.12±0.26	1.75±0.44	<0.001**

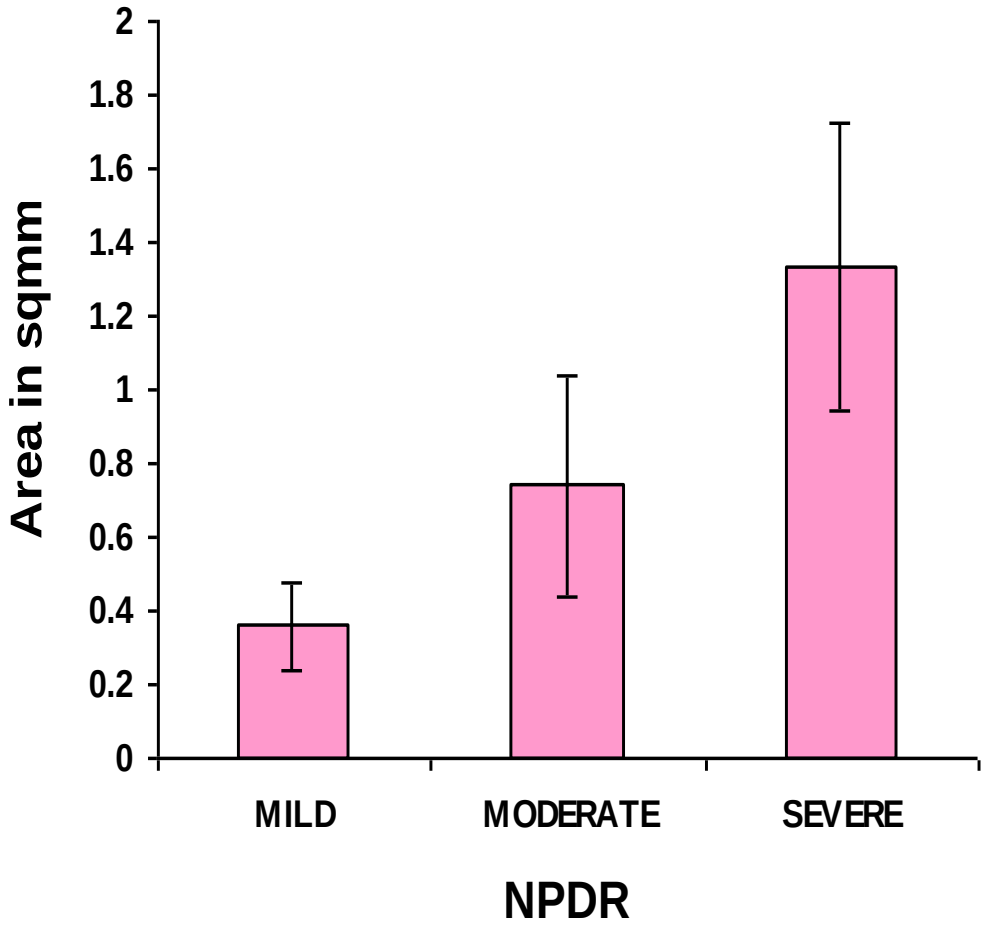


Fig. 4

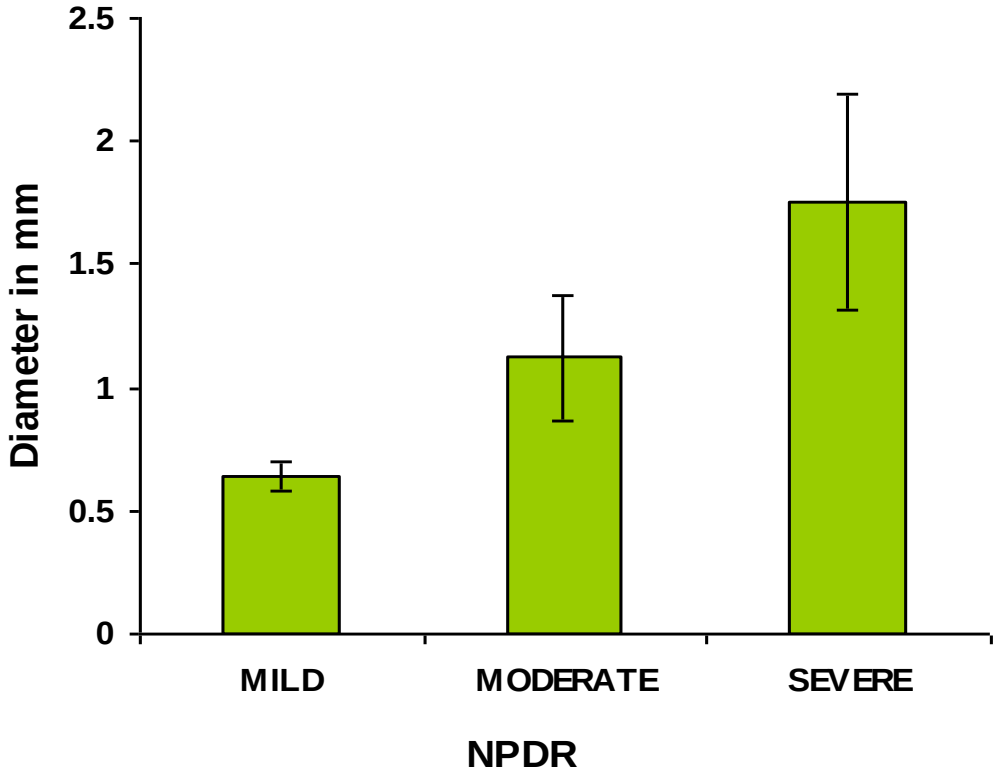


Fig. 5

Both FAZ diameter and area show a strong correlation with stage of diabetic retinopathy ($p<0.001$).

Table 3: Correlation of FAZ Diameter with the 3 stages of NPDR

FAZ diameter	NPDR		
	Mild	Moderate	Severe
GD 1	0	0	0
GD 2	10(100.0%)	0	0
GD 3	0	10(100.0%)	10(100.0%)
Total	10	10	10

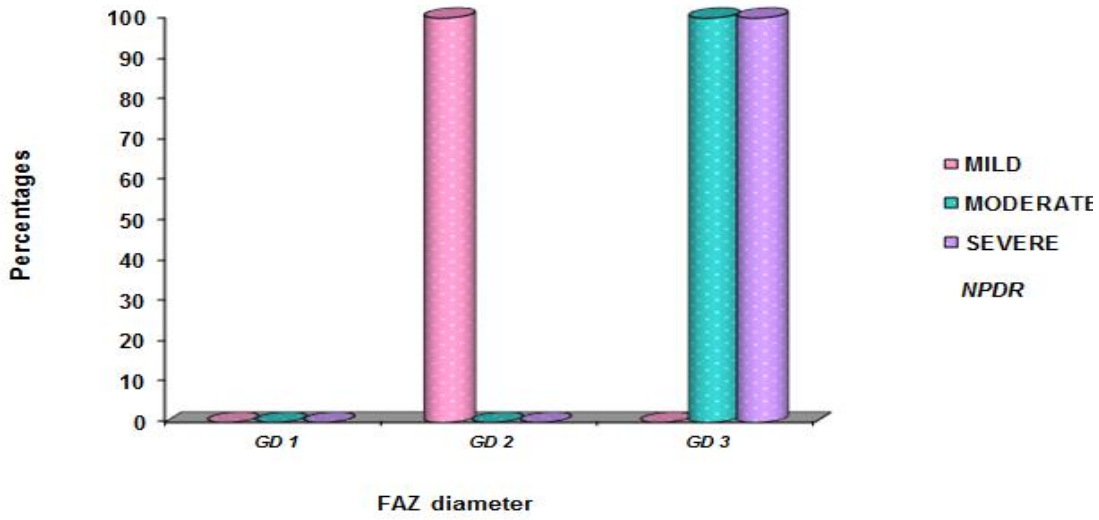


Fig. 6

Grade 2 FAZ Diameter (350-750um) was associated with mild NPDR whereas Grade 3 FAZ Diameter (>750um) was significantly associated($p<0.001$) with moderate and severe NPDR.

Table 4: Correlation of FAZ Outline with the 3 stages of NPDR

FAZ outline	NPDR		
	Mild	Moderate	Severe
GD 1	10(100.0%)	4(40.0%)	3(30.0%)
GD 2	0	6(60.0%)	5(50.0%)
GD 3	0	0	2(20.0%)
Total	10	10	10

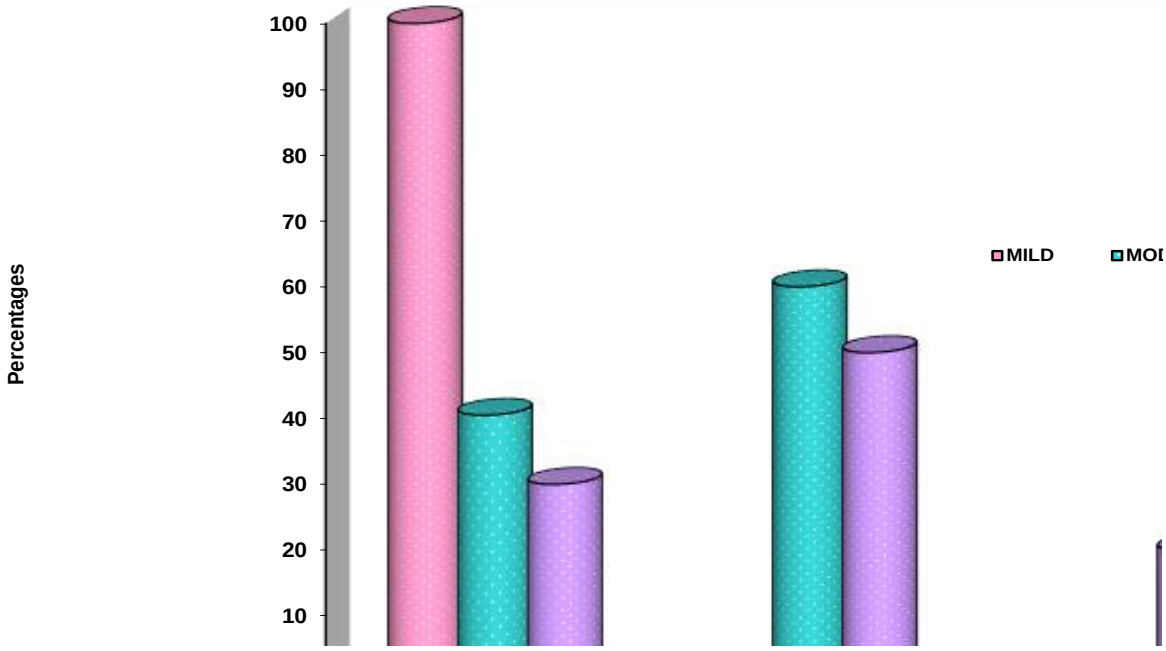


Fig. 7

In severe NPDR 50% patients had grade 2 outline, 20% had grade 3 outline and in moderate NPDR 60% patients had grade 2 outline. Thus, greater incidence of macular ischemia was seen in patients with more advanced forms of NPDR($p=0.003$) .

Table 5: Correlation of FAZ-diameter with FAZ –outline

FAZ diameter	FAZ-outline		
	GD 1	GD 2	GD 3
GD 1	0	0	0
GD 2	10(58.8%)	0	0
GD 3	7(41.1%)	11(100%)	2(100%)
Total	17	11	2

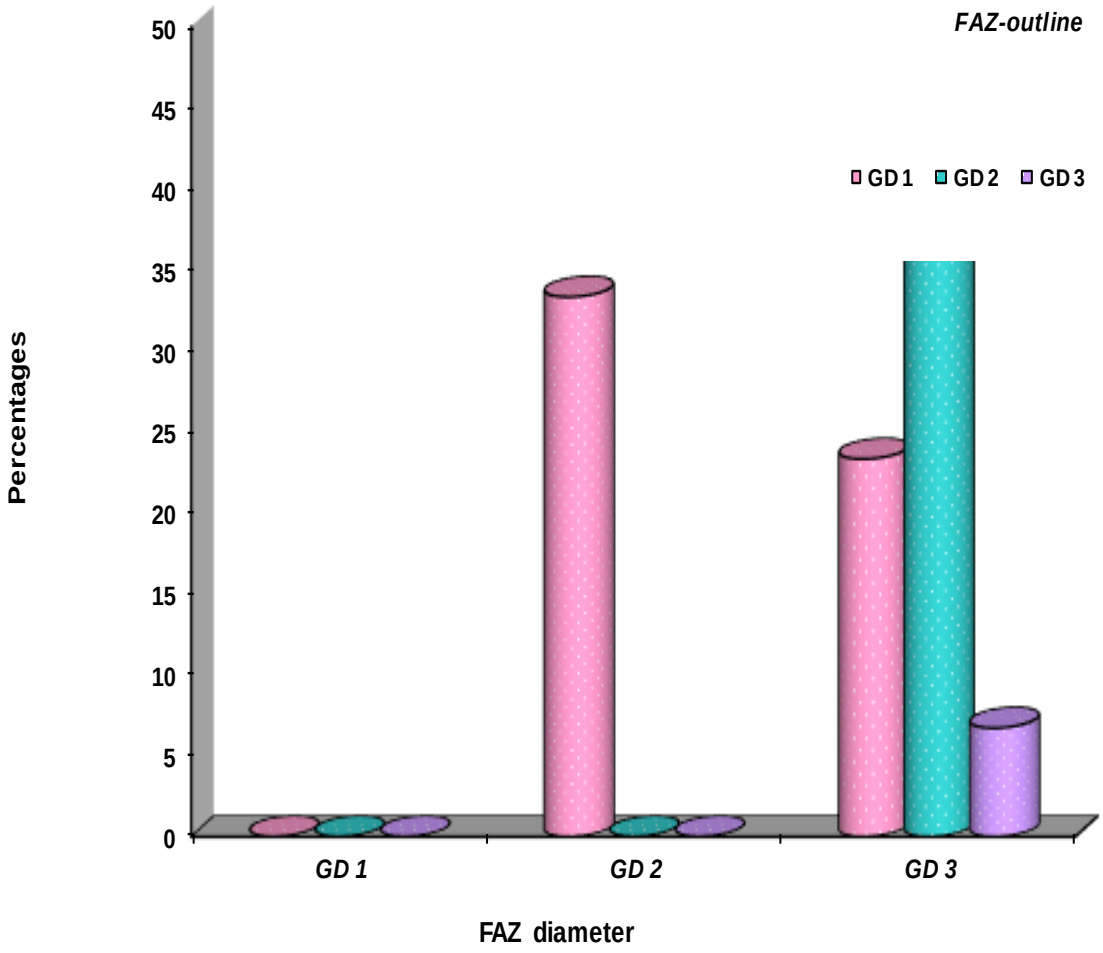


Fig. 8

All patients with grade2 and grade 3 FAZ outline had grade 3 FAZ diameter in our study. FAZ diameter is significantly associated with FAZ outline in our study (p=0.001).

Table 6: Morphological changes seen in FAZ in FFA in the 3 stages of NPDR

Morphological changes in FAZ on FFA	NPDR			p value
	Mild (n=10)	Moderate (n=10)	Severe (n=10)	
Normal	6 (60.0%)	0	0	0.001**
Budding	4(40.0%)	10(100.0%)	10(100.0%)	0.001**
Irregular margin	0	6(60.0%)	9(90.0%)	<0.001**
Erosions	0	2(20.0%)	6(60.0%)	0.011*
Widening of intercapillary spaces	0	2(20.0%)	6(60.0%)	0.011*

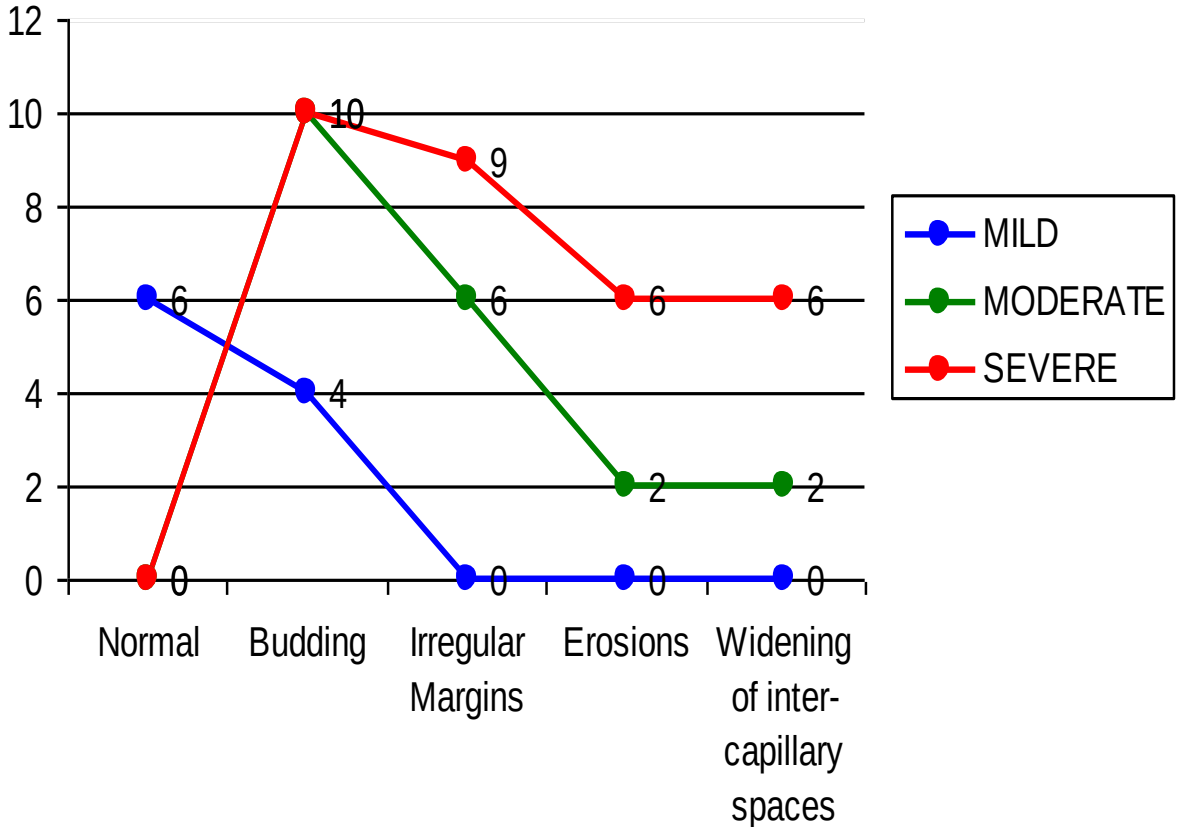


Fig. 9

Majority (60%) of patients with mild NPDR did not show any changes in the FAZ. Budding into the FAZ was seen in 40% of patients with mild NPDR and in all patients with moderate and severe NPDR (p=0.001). Irregular margins were seen in 60% of patients moderate NPDR and 90% of patients with severe NPDR which was strongly significant (p<0.001). Erosions were seen in 20% of patients with moderate NPDR and 60% of patients with severe NPDR. Widening of intercapillary spaces was also seen in 20% patients with moderate NPDR and 60% of cases with severe NPDR.

The above analysis showed a extremely strong positive correlation between the presence of morphological abnormalities like budding, irregular margins, erosions and widening of intercapillary spaces with increased severity of NPDR. A significant correlation (p<0.001) was found between the presence of the morphological abnormalities (budding, irregular margins, erosions and widening of intercapillary spaces) in 3 or more quadrants and severe NPDR indicating the progression of morphological changes with increasing severity of retinopathy.

Table 7: Correlation of FAZ-diameter with Visual acuity

FAZ diameter	Visual acuity		
	6/6-6/12	6/18-6/60	<6/60
GD 1	0	0	0
GD 2	10	0	0
GD 3	16(61.5%)	3	1
Total	26	3	1

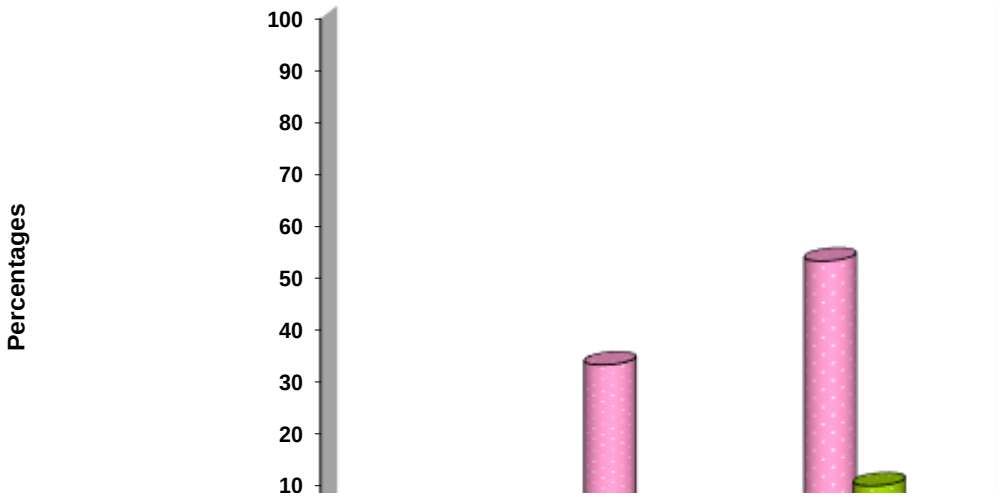


Fig. 10

16(61.5%) patients with BCVA 6/6-6/12 had grade 3 FAZ diameter (>750um). FAZ diameter is not significantly associated with Visual acuity (p=0.688) in our study.

Table 8: Correlation of FAZ-outline with visual acuity

FAZ Outline	Visual acuity		
	6/6-6/12	6/18-6/60	<6/60
GD 1	17(65.3%)	0	0
GD 2	9(34.6%)	2(66.6%)	0
GD 3	0	1(33.3%)	1(100%)
Total	26	3	1

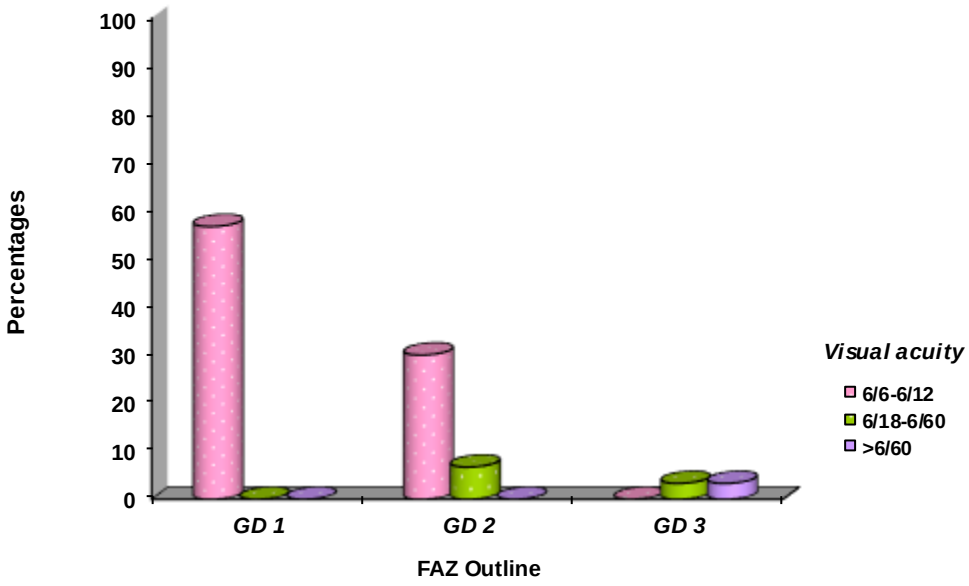


Fig. 11

65.3% of patients with BCVA 6/6-6/12 did not have any outline abnormalities and 34.6% of these patients had destruction of <1/2 of the circumference of the FAZ (grade 2). 66.6% of patients with BCVA 6/18-6/60 had grade 2 changes and 33.3% had grade 3 changes in outline. All patients who had poor BCVA (<6/60) had >1/2 circumference destruction of FAZ (grade 3). FAZ outline is significantly associated with BCVA with p=0.002 in our study.

Table 9: Correlation of FAZ diameter with associated comorbidities: Hypertension, Lipid and Renal profile

FAZ-diameter	HTN		LIPID		RENAL	
	Absent	Present	Normal	Abnormal	Normal	Abnormal
GD 1	-	-	-	-	-	-
GD 2	4(33.3%)	6(33.3%)	10(38.4%)	0	10(40%)	0
GD 3	8(66.6%)	12(66.6%)	16(61.5%)	4(100%)	15(60%)	5(100%)
Total	12	18	26	4	25	5
p value	1.000		0.272		0.140	

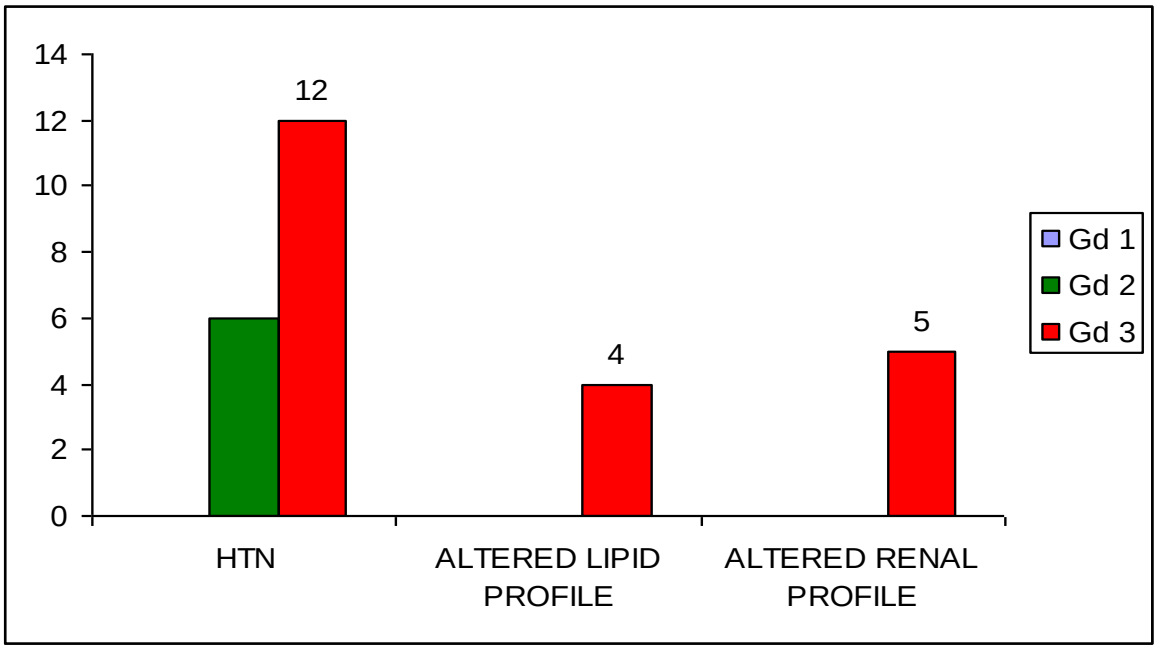


Fig. 12

In our study (60%) of patients had hypertension, out of which 33.3% had grade 2 and 66.6% had grade 3 FAZ diameter(p=1.0). 13.3% of all patients had altered lipid profile and all had grade 3 FAZ diameter(p=0.272). 16.6% had altered renal profile (p=0.14). Thus there was no statistically significant association between FAZ diameter and associated comorbidities.

Table 10: Correlation of FAZ outline in relation to Hypertension, Lipid and Renal profile

FAZ-Outline	HTN		LIPID		RENAL	
	Absent	Present	Normal	Abnormal	Normal	Abnormal
GD 1	6(50%)	11(61.1%)	16(61.5%)	1(25%)	17(68%)	0
GD 2	5(41.6%)	6(33.3%)	8(30.7%)	3(75%)	8(32%)	3(60%)
GD 3	1(8.3%)	1(5.5%)	2(7.6%)	0	0	2(40%)
Total	12	18	26	4	25	5
P value	0.852		0.345		0.001**	

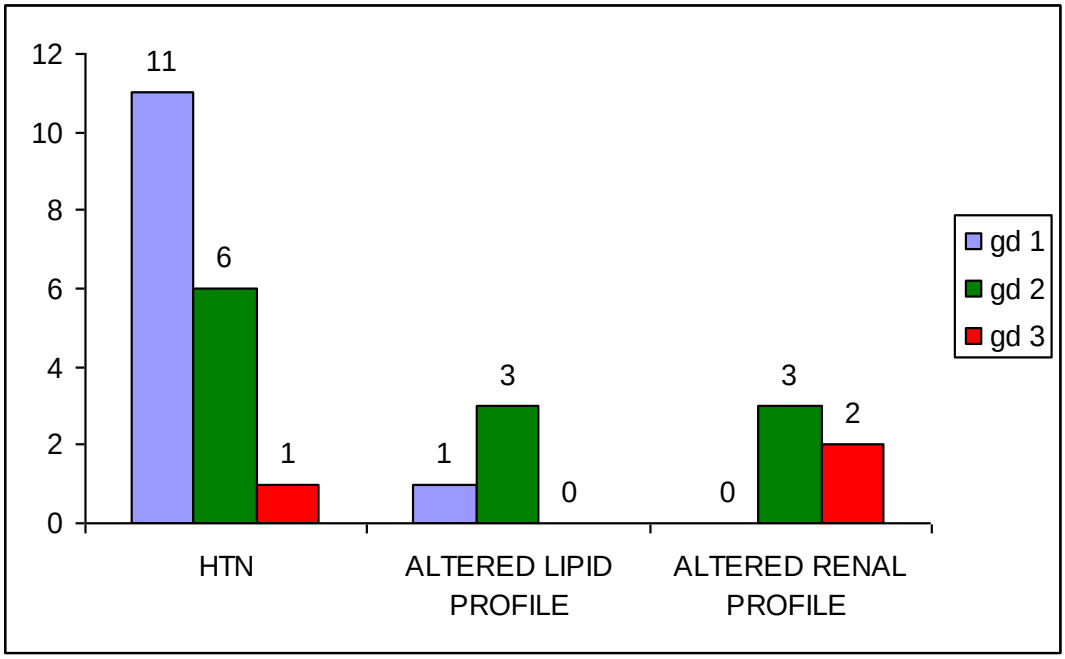
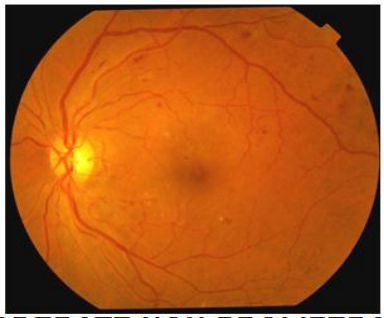


Fig. 13

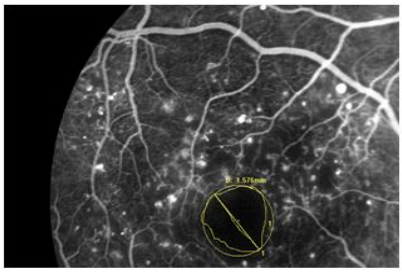
61.1% patients with hypertension had grade 1, 33.3% had grade 2 and 5.5% had grade 3 FAZ outline (p=0.852) changes. Thus, no statistically significant association was found between hypertension and FAZ outline.
75% of patients with hyperlipidemia had grade 2 FAZ outline and rest had normal FAZ outline. Thus no significant correlation was found between hyperlipidemia and FAZ outline changes in our study (p=0.345).
16.6% had altered renal profile in our study of which 60% had grade 2 FAZ outline changes and 40% had grade 3 FAZ outline changes. Thus a significant association was found between FAZ outline and nephropathy (p=0.001).

FUNDUS RETINAL CAMERA –CANON

FLUORESCEIN DYE



MODERATE NON PROLIFERATIVE DIABETIC RETINOPATHY



FOVEAL AVASCULAR ZONE- OUT LINE, LONGEST DIAMETER AND AREA

Fig. 14

FOVEAL AVASCULAR ZONE- OUT LINE, LONGEST DIAMETER AND AREA

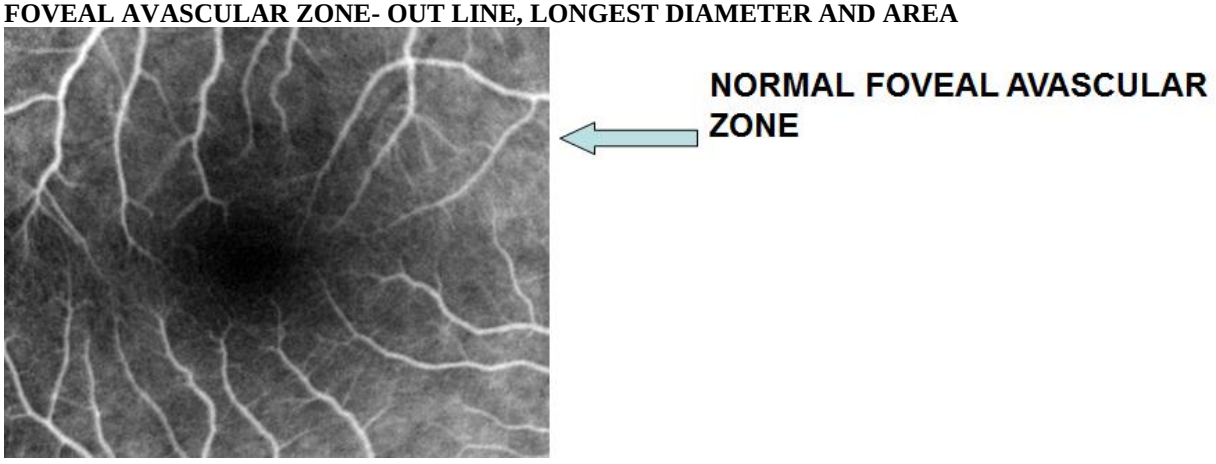


Fig. 15

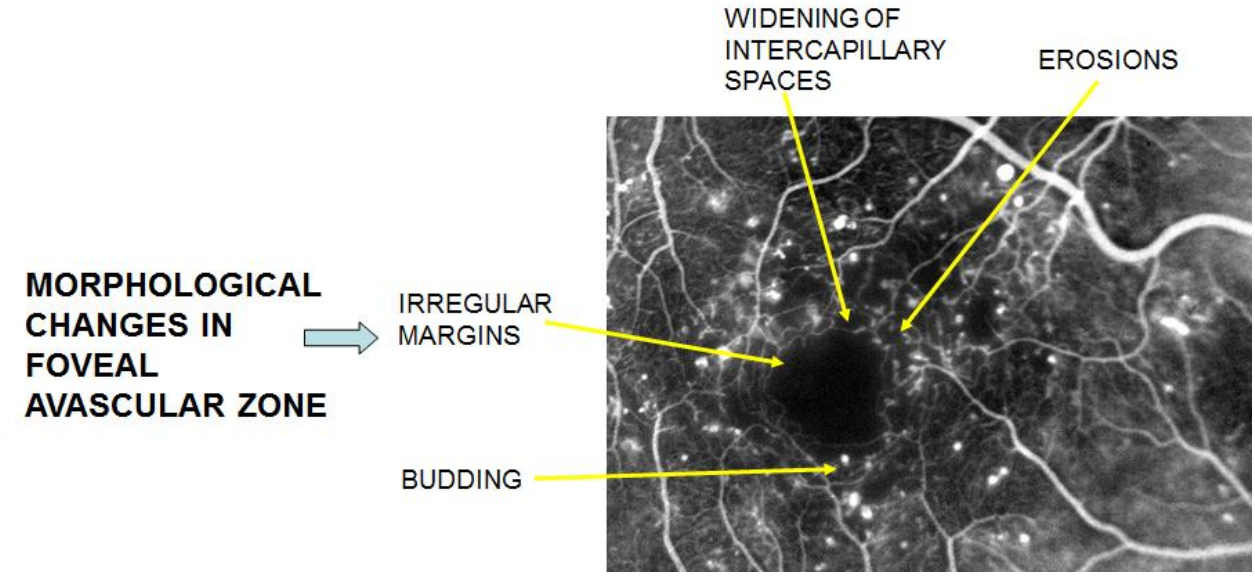


Fig. 16

DISCUSSION

Diabetic Retinopathy (DR) is one of the leading causes of blindness worldwide.[3] Tight metabolic control has been shown to significantly decrease risk of development as well as progression of DR and remains the cornerstone in medical management of DR.[3]

Foveal avascular zone is a region in the macula that provides highest visual acuity, contrast vision and color vision.[4] In diabetics, alteration in the retinal microvasculature leads to occlusion of the perifoveolar capillaries. This lack of perfusion leads to an increased size of the FAZ on FFA. These changes progresses as the stage of retinopathy advances.

The commonest cause of visual loss in diabetic retinopathy is diabetic maculopathy which includes macular edema and macular ischemia. Macular ischemia is due to macular capillary occlusion in the posterior pole more specifically at the level of capillary network defining the FAZ. Assessing the severity of ischemia in diabetic patients could thereby lead to better understanding and identification of ischemic diabetic Maculopathy.[9] FFA is the most important tool for assessing macular ischemia as it gives direct evidence of capillary non-perfusion in the perifoveal area.[9]

In this study, the severity of perifoveal capillary abnormalities was assessed by classifying the diameter and outline of FAZ into 3 grades based on a study done by Sheriff et al[9] using intravenous FFA. The FAZ was also examined for presence of any morphological changes indicative of macular ischemia like irregular margins, budding, erosions and widening of intercapillary spaces.[5]

In our study, majority of patients (53%) were in the age group of 51 to 60 years. The mean age of patients in our study was 58.7±2.33 years. 80% of them were males. Correlating diabetic retinopathy to the type of diabetic they belong,100% of patients with mild NPDR had type 2 DM, 70% patients with moderate NPDR had type 2 DM and 80% of patients with severe NPDR had type 2 DM. Distribution of type of DM was not statistically significant across the various stages of NPDR.

Duration of DM

In our study, the duration of DM showed a strong correlation with the stage of retinopathy. A disease duration of >10yrs showed a statistically significant correlation with more severe grades of retinopathy [Moderate (60%) and Severe (60%) NPDR] with p=0.005. All the cases of Mild NPDR had a disease duration of <10 years further reinforcing the correlation between the duration and stage of retinopathy. This is in concurrence with the findings of the WESDR study group which found a direct correlation between the duration of DM and severity of retinopathy.

Association of DR with BCVA

In our study, 40% of patients with severe NPDR had BCVA <6/18 which was statistically significant. All eyes with mild and moderate NPDR had BCVA better than 6/12. DR was reported to be positively correlated with moderate visual loss (6/18 – 6/60) in the study done by Rani PK et al.

Glycemic control

In our study poor (30%) glycemic control is significantly associated with Severe NPDR (p<0.001). The Diabetes Control and Complications Trial (DCCT) study has illustrated 35% to 40% reduction in risk of retinopathy progression for every 10% decrease in HbA_1C.

Association of diabetic retinopathy with hypertension

The United Kingdom Prospective Diabetic Study (UKPDS) study has clearly illustrated that hypertension is a major risk factor for the development and progression of DR.[22]

According to Rani PK et al elevated systolic blood pressure is one of the risk factors independently associated with presence and severity of DR. O Arend et al[17] in their study suggest that the capillary closure associated with DM is so dominant that the arterial HTN results in no additional detectable capillary closure.

However, Norgaard et al[23] found that arterial hypertension per se is not associated with increased retinal changes but it may worsen these changes in pts with clinically apparent nephropathy.

In our study, 60% of mild, 40% of moderate and 80% of patients with severe NPDR had associated hypertension which was not statistically significant across the 3 stages of NPDR. Thus no increase in rate of progression of DR in patients with associated hypertension was noted which is similar to the studies done by Norgaard et al[23], West KM et al[28], Chen MS et al[24] and Klein R et al.[25]

Association of DR with hyperlipidemia

It has been proven that total cholesterol and triglycerides are higher in patients with DR[26] by Conrath J et al.[4] Also increased levels of total cholesterol have been found to be associated with macular exudates in DR.[19,20] However, some studies have found no link between them and DR.

In our study, 40% of patients with moderate NPDR had altered lipid profile which was statistically significant.

Association of DR with Nephropathy

Presence and severity of DR has been reported to be strongly associated with proteinuria in both type 1 and 2 DM. Therefore, severity of DR might be a common link between macular ischemia and nephropathy. Although 20% of moderate and 30% of eyes with severe NPDR showed an altered renal profile in the form of elevated blood urea, serum creatinine and proteinuria in our study the association between the stage of retinopathy and altered renal profile was not statistically significant. This is probably because we haven't included patients with PDR in our study.

FAZ ANALYSIS

In our study, we measured the greatest horizontal diameter of the FAZ and the area of the FAZ.

1) FAZ Diameter

The mean FAZ diameter in patients with mild, moderate and severe NPDR was 0.64±0.06, 1.12±0.26, 1.75±0.44mm respectively and a strong correlation (p<0.001) was seen between the FAZ diameter and stage of retinopathy. FAZ diameter of >750um (grade 3) was significantly associated with more advanced grades of retinopathy (moderate and severe NPDR). This is in contrast to a study by Bresnick et al[5] where the mean FAZ diameter was 0.79mm in patients with diabetic retinopathy. The FAZ dimensions compared with non-diabetic controls were statistically significant for longest diameter, mean diameter and circumference. In a study done by Saini VK et al[27] significant increase of the mean FAZ diameter of 0.6 to 0.7 mm was noted in 60.9% of diabetic retinopathy cases in comparison to other retinal and choroidal diseases in the study.

2) FAZ area

A strong positive correlation (p<0.001) was seen between increasing severity of retinopathy and the area of FAZ in our study.

The mean FAZ areas in mm^2 in different stages of DR in various other studies are given in the table below:

Various studies by	Mild NPDR	Moderate-severe NPDR	PDR
Conrath J et al	0.303±0.19	0.419±0.25	0.608±0.413
Conrath J et al[5]	0.30	0.42	0.61
Arend O et al[11]	0.318	0.513	0.590
Mansour et al[6]	0.737	1.001	0.866

In our study, the mean FAZ area in different stages of NPDR was,

NPDR	Mild	Moderate	Severe
Mean FAZ Area(mm^2)	$0.36mm^2$±0.12	$0.74mm^2$±0.30	$1.33mm^2$±0.39

In our study, the FAZ area in mild NPDR was comparable to the data published by Conrath et al[4,16] and Arend et al.[11] However, the FAZ areas in moderate and severe NPDR in our study were higher than those reported by the above authors. Our data was however similar to the data published by Mansour et al.[6]

3) FAZ outline

Conrath J et al[16] reported that abnormalities of FAZ outline correlated well with severity of retinopathy (p=0.003). In our study, 11 patients with moderate to severe NPDR (55%) had a grade 2 FAZ outline change which is almost comparable with the study done by Conrath et al (43.3%). 2 patients with moderate to severe NPDR (10%) showed >1/2 FAZ outline destruction, whereas Conrath Jet al[16] reported similar changes in 43.4% of patients.

Thus, an increased destruction of the perifoveal capillary network was significantly associated with increased severity of retinopathy with grades 2 and 3 FAZ outline showing a significant association with moderate and severe NPDR respectively.

All the above findings in our study illustrate a greater incidence of macular ischemia in patients with more advanced forms of NPDR namely moderate and severe NPDR. Our study, also showed a strong positive correlation between FAZ outline and FAZ diameter (p<0.001).

4) Abnormal FAZ patterns

Majority (60%) of patients with mild NPDR did not show any changes in the FAZ. Budding into the FAZ was seen in 40% of patients with mild NPDR and in all patients with moderate and severe NPDR (p=0.001). Irregular margins were seen in 60% of patients moderate NPDR and 90% of patients with severe NPDR which was strongly significant (p<0.001). Erosions were seen in 20% of patients with moderate NPDR and 60% of patients with severe NPDR. Widening of intercapillary spaces was also seen in 20% patients with moderate NPDR and 60% of cases with severe NPDR.

A significant correlation was also found between the presence of the above morphological abnormalities in 3 or more quadrants and severe NPDR indicating the progression of morphological changes with increasing severity of retinopathy.

Bresnick et al[5] reported that considerable variation in FAZ dimensions in non-diabetics and diabetics made the diagnosis of FAZ abnormality in a diabetic patient difficult if based on size alone and that irregular FAZ margins, erosions of parafoveal capillaries, intrusion of dilated capillary buds into FAZ, presence of arteriolar stumps at FAZ margins to be more reliable indicators of macular ischemia. Shulka et al[13] also reported that macular ischemia based on the criteria laid down by Bresnick[5] to be more common in severe stages of DR.

5) Correlation of FAZ diameter with BCVA

Our study, however did not find a correlation between BCVA and the FAZ diameter with 16(61.5%) patients with BCVA 6/6-6/12 showing FAZ diameter >750um.

Saini VK et al[27] reported decrease in BCVA to<6/18 with increase in FAZ diameter in the range 0.6mm to 0.7mm in patients with DR in its study . In our study, 40% of patients had FAZ diameter in the range of 0.6 to 0.7mm with BCVA between 6/6 to 6/12.

6) Correlation of FAZ outline with BCVA

The FAZ outline however showed a strong correlation with BCVA. 65.3% of patients with BCVA 6/6-6/12 did not have any outline abnormalities and 34.6% of these patients had destruction of <1/2 of the circumference of the FAZ (grade 2 outline). In contrast, 66.6% of patients with BCVA 6/18-6/60 had grade 2 FAZ changes and 33.3% had grade 3 FAZ changes in outline. All patients who had poor BCVA (<6/60) had >1/2 circumference destruction of FAZ (grade 3 outline).

In a study done by Arend O et al[28] DR patients with BCVA of <20/50 revealed a significantly enlarged FAZ (73%) when compared with DR patients with unaffected visual acuity and was almost triple the size on comparison with FAZ of healthy subjects. Thus, a significant correlation of reduced BCVA with enlarged FAZ area and PIA in diabetic patients was reported in their study which supports the data in our study.

However, no apparent correlation between FAZ dimensions and BCVA was noted in studies done Mansour et al[6] and Bresnick et al.[5]

7) Correlation of FAZ morphological changes with Hypertension

In our study (60%) of patients had hypertension, out of which 33.3% had grade 2 and 66.6% had grade 3 FAZ diameter (p=1.0) changes. 61.1% patients with hypertension had grade 1, 33.3% had grade 2 and 5.5% had grade 3 FAZ outline (p=0.852) changes which was not statistically significant. Thus, no significant association of hypertension with macular ischemia was found which is comparable to the study done by Shulka D et al.[13]

In a study done by Arend O et al[17] no significant difference in FAZ area between diabetic patients with

($0.319mm^2$) and without hypertension($0.363mm^2$) was noted which is comparable to our study where mean FAZ area in DR patients was $0.802mm^2$ with associated hypertension and $0.825mm^2$ in those without hypertension. Mansour et al[6] found no apparent correlation between FAZ area and systemic HTN ($p<0.2$). Conrath J et al[4] did not find hypertension to influence macular microcirculation. This might be due to the fact that the patients were under anti-hypertensive medication.

Increased rate of progression of diabetic retinopathy with associated hypertension is seen in UKPDS study[22] as well as in studies done by Chase et al[29], Janka HU et al and Cignarelli M et al.[30]

8) Correlation of FAZ morphological changes with Glycemic control

Among all the patients in our study, 10% patients had poor glycemic control which was significantly associated with Severe NPDR ($p<0.001$), of which 66.6% had grade 3 FAZ outline distortion and 33.3% had grade 2 FAZ outline distortion and all had grade 3 FAZ diameter .Thus a positive correlation was found between perifoveal capillary loss and HbA_1C level similar to the study done by Sanders et al and Doft et al. However, Conrath J et al[4] found no significant correlation between FAZ (area and outline) and HbA_1C.

9) Correlation of FAZ morphological changes with altered renal profile

Amongst all the patients in our study 16.6% had altered renal profile of which 60% had grade 2 FAZ outline distortion and 40% had grade 3 FAZ outline distortion. All had grade 3 FAZ diameter ($p=0.140$). Thus, a significant association was found between macular ischemia and nephropathy ($p=0.001$) as reported before by Shulka D et al[13] and Bresnick et al.[18]

Also a statistically significant reduction in occurrence of diabetic nephropathy with intensive blood glucose control is illustrated in DCCT study.

10) Correlation of FAZ morphological changes with altered lipid profile

In our study, 13.3% patients had altered lipid profile and All had grade 3 FAZ diameter ($p=0.272$) of which 75% had grade 2 FAZ outline ($p=0.345$) and rest had normal FAZ outline. Thus, no significant correlation between hyperlipidemia and presence of macular ischemia was noted in our study which is similar to the study done D Shukla et al.[13]

CONCLUSION

All patients with diabetes invariably develop microangiopathy as the disease progresses. Chronic hypoxia leads to tissue ischemia in the retina and other end organs. Therefore diagnosis of macular ischemia should alert us to the presence of systemic abnormalities like nephropathy and prompt us to investigate further.

FFA plays a significant role in analysis of morphological changes in the FAZ like irregular margins, erosions of parafoveal capillaries, presence of arteriolar stumps at FAZ margins and widening of intercapillary spaces which otherwise would have been missed out on clinical examination in patients with or without significant visual function loss.

Macular ischemia thus appears to be a marker for the severity of diabetic retinal disease and other systemic disorders like nephropathy. As is proven in our study the presence of structural and morphologic changes in the perifoveal circulation correlates significantly with changes in visual function and presence of metabolic disorders like nephropathy.

However, hypertension and hyperlipidemia may not have any direct effect in perifoveal capillary changes as illustrated in our study.

Effective screening of all diabetic patients may aid in early diagnosis of diabetic maculopathy and nephropathy and thereby prevent the associated ocular and systemic morbidity and mortality.

Also with the various studies being made in the treatment of retinal vascular disorders, a comprehensive classification system is necessary for macular ischemia, for its early diagnosis in order to appropriately target patients for further intervention.

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