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Research Article

Correlation Between Fundus Fluorescein Angiography (FFA), Optical Coherence Tomography (OCT) and Visual Acuity in Eyes with Broken Foveal Avascular Zone (FAZ)

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Abstract

Purpose: To identify the correlation between the broken foveal avascular zone (FAZ) on fundus fluorescein angiography (FFA) with the outer retinal changes on the optical coherence tomography (OCT) and relationship with visual acuity.

Methods: The study included the patients with diabetic retinopathy, non-proliferative and proliferative, with broken FAZ on FFA, and were compared with the controls selected from the eyes without retinopathy and intact FAZ. The OCT scanning with enhanced depth imaging (EDI) through the area of broken FAZ was reviewed.

Results: Thirty eyes (mean age 51+12.92 years) with broken FAZ were included-18 eyes showed broken inner segment- outer segment (IS-OS) on OCT (p=0.21). Mean diabetic age was 8.3+4.01 years. Eight eyes in the study group had >20/30 best corrected visual acuity (p=0.26). Macular thickness and visual acuity did not have a linear correlation. The duration of diabetes had a significant correlation with broken IS-OS junction (p=0.004).

The odds of poor vision with broken FAZ were 2.5 (95% CI 0.5-12.4). The positive predictive value (PPV) of disrupted IS-OS junction in broken FAZ was 47.37% (95% CI (range 30.98% to 64.18%) and the negative predictive value (NPV) of intact IS-OS junction in broken FAZ was 50% (95% CI range 29.12% to 70.88%). The combined PPV of poor vision (<20/40) and longer diabetic duration (>9 years) was 88.89% (range 51.75% to 99.72%) and the NPV was 100% (range 71.51% to 100%).

Conclusion: Disrupted IS-OS junction could indicate an ischemic macula, but correlation with visual acuity is important.

Keywords: FAZ:Foveal avascular zone; FFA:Fundus fluorescein angiography; IS-OS:Inner segment-Outer segment; OCT:Optical coherence tomography.

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Introduction

The integrity of the foveal avascular zone (FAZ) reflects the anatomic and functional integrity of the fovea [1]. In a healthy eye the FAZ is round or oval around the fovea center; it measures 500-600μm in diameter and is best visualized in the early phase of fundus fluorescein angiography (FFA). Its hypofluorescence appearance in FFA owes to the avascularity in this area and presence of pigments that block the background choroidal fluorescence [2]. Breaking of FAZ occurs in many retinal vascular diseases, but chiefly, in diabetic retinopathy and retinal vascular disorders. The FFA is the current gold standard to identifying the FAZ integrity. This is an invasive procedure and is not completely risk free [3]. Optical Coherence Tomography Angiography (OCTA) is newly developed and noninvasive technology that does not require intravenous injection and can be used to investigate several diseases like diabetic retinopathy. OCTA can also be applied to identify preclinical diabetic retinopathy before the disease affects eyes [4].

Recent study done by Hideki and his co-workers observed the greater variation of FAZ over its shape using OCTA [5]. Although OCTA is widely being used in recent days, but it has few drawbacks like motion error which leads to vessels discontinuity. In our study we have used FFA (as a part of management plan) to evaluate the FAZ within the initial phase and spectral domain optical coherence tomography (OCT) to image the outer retina (the retinal pigment epithelium to outer nuclear layer, supplied by the choroidal circulation) and the inner retina (outer plexiform layer to inner limiting membrane, supplied by the retinal circulation), and correlated with the FFA and the visual acuity. The objective of the study is to identify the OCT characteristics of an intact and broken FAZ without FFA in eyes with diabetic retinopathy.

Materials and Methods

This study recruited patients with diabetic retinopathy, either non-proliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR), with broken FAZ on a routine angiogram done as part of their management. The study was approved by the institutional ethics committee and followed the tenants of the Declaration of Helsinki. The eyes with hazy media due to any cause, myopia more than 4 Dsph, hard exudates at the foveal region, macular scar, delayed arm- to- retina or artery-to- vein filling time and patients who refused to sign the consent form were excluded. The age matched control eyes included the eyes with intact FAZ. These were the 6 fellow eyes with intact FAZ, four fellow eyes of patients with central serous chorioretinopathy and five eyes with unremarkable fundus.

All patients recruited into the study received a comprehensive eye examination. This included history of diabetes and present status, visual acuity measured by ETDRS logMAR chart at 4-meter, intraocular pressure by Goldmann applanation tonometer and dilated (tropicamide 1%) fundus examination by indirect ophthalmoscope with +20D lens and slit lamp biomicroscopy with +90D lens. The best corrected vision of 20/20 to 20/30 (log 0.0 to 0.2) level was defined as good visual acuity. FF 450 plus IR (Zeiss, Dublin, USA) was used for both fundus photograph and FFA. Cirrus HD-OCT (Zeiss, Dublin, USA) was used for OCT recording.

The FFA was done by injecting 5 ml of 20% Sodium fluorescein (Na Fl) dye into the ante cubital vein and the fundus angiographs obtained at 20-25 seconds were analyzed. The angiograms of the central retina that showed the FAZ were selected, and the 6 mm fundus view was magnified to make the FAZ more prominent. Areas of both intact and broken FAZ were measured manually by free hand drawing.

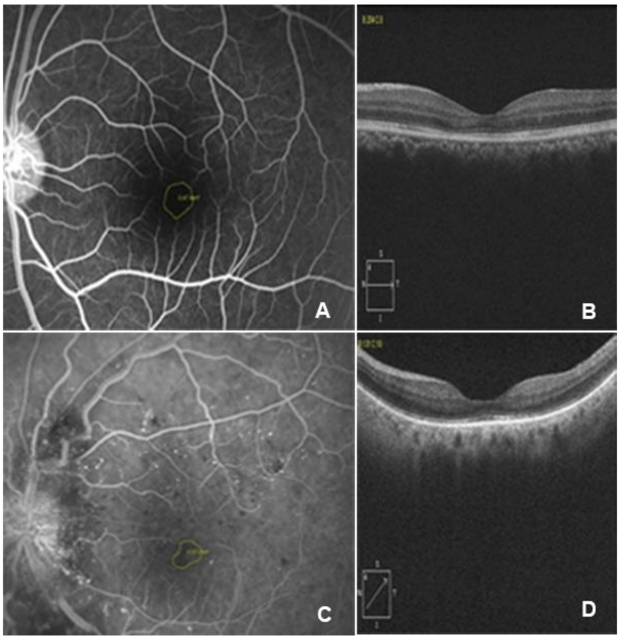

Figure 1: FAZ and corresponding OCT.

Cirrus SD-OCT scanning was performed along the area of distortion with HD 5-line raster scan. Signal strength of 6 or more was included in this study. Macular thickness was analyzed by the macular cube 512x128 protocol. HD 5-line raster was performed over the broken FAZ seen on the FFA. Orientation of the raster line was maintained after observing the angiographic photograph within 30 seconds.

We noted the IS-OS junction pattern over the distorted region in eyes wherever this was distorted (Figure 1: FFA (A) showing intact FAZ and corresponding OCT (B) represents intact IS-OS junction. broken FAZ (C) showing broken IS-OS line on OCT (D). We defined IS-OS junction broken when this junction appeared irregular or appeared very faint; and IS-OS junction intact when the line was properly visible. Intact FAZ was defined if the centre of the fovea is maintaining the circular architecture and if any of the area is irregular and therefore not showing proper circular structure was considered to be broken. Similarly the term "intact" IS-OS junction was made when the line is prominently continuous in the absence of macular edema and "disrupted" was defined if discontinuation was observed (Figure 2: broken FAZ on FFA (A,C,E) showing broken IS-OS junction at the distorted area (B), intact IS-OS margin (D) and faint IS-OS line (F).

OCT thickness of the foveal region was taken to consider the foveal thickness. Gray scale OCT images were taken for the best contrast effect. FFA identified two groups of broken FAZ (study group) and intact FAZ (control group). Both FFA and OCT findings were weighed against the duration of known diabetes and best corrected visual acuity.

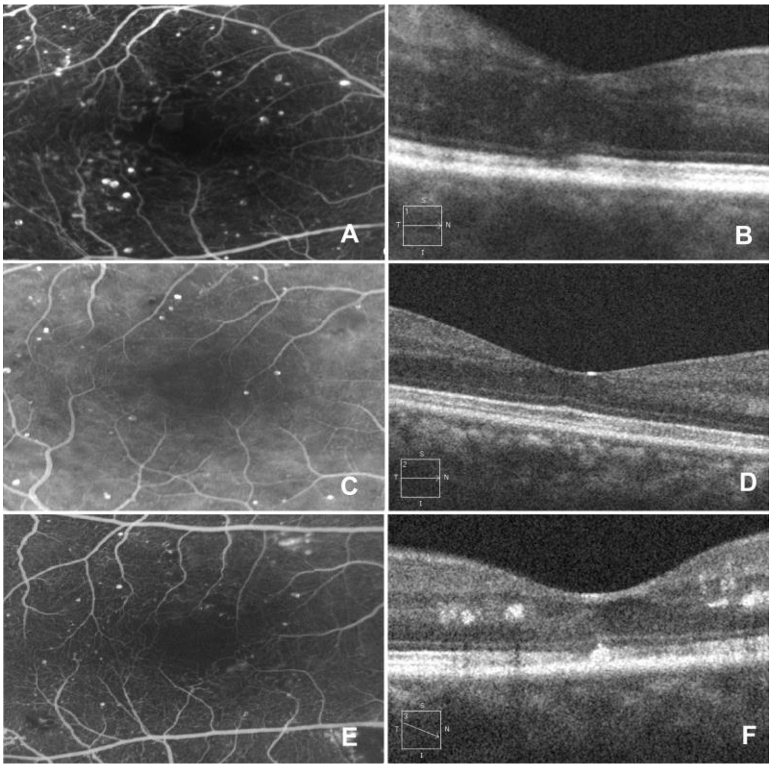

Figure 2: Correlation between broken FAZ and features on OCT.

Statistical Analysis

This included descriptive statistics such as mean, median, confidence interval and standard deviation, and inferential statistics such as Odds ratio, Positive Predictive Value (PPV), Negative Predictive Value (NPV). Medcalc software was used for statistical calculation.

Results

The study group consisted of 30 eyes of 20 patients. All study patients had type 2 diabetes mellitus. Mean age was 51+12.92 years. Eighteen eyes had disrupted IS-OS junction on OCT and 12 had intact IS-OS junction. Mean macular thickness of broken FAZ eyes was 286.78+120.75 µm (range 250.52 µm to 323.04 µm; 90% confidence interval 88.13-485.43). The control group consisted of 32 eyes of 20 patients. Mean age was 49+7.6 years. Mean macular thickness was 225.90+13.51 µm (range 221.97 µm to 229.83 µm; 90% confidence interval, 213.34-232.85). Macular thickness was estimated at the region of fovea in all cases. Mean area of the broken FAZ was 0.51+0.2 mm^2 (range 0.43 mm^2 to 0.58 mm^2; 90% confidence interval, 0.15-0.83) and control group of intact FAZ was 0.42 + 0.071 mm^2 (range 0.44 mm^2 to 0.57 mm^2; 90% confidence interval, 0.45-0.55). All 32 eyes in the control group had intact FAZ and had a well demarcated IS-OS junction. Eighteen of 30 study eyes (60%) had broken IS-OS junction; this was statistically not significant. (p=0.21). All eyes showed intact ELM and there is no change in thickness of RPE-CC complex, however we could not make much details on interdigitation line and we did not include choroidal thickness because of poor delineated margin. Eight eyes (26%) in the study group had best-corrected vision of 0.01logMAR or more; this included 3

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(16.66%) eyes with disrupted IS-OS junction and 5 (41.66%) eyes with intact IS-OS junction eyes (Table 1: Relationship between IS-OS junction and visual acuity in eyes with broken FAZ). Between them they were not statistically significant (p=0.26). The odds of poor vision with broken IS-OS junction were 2.5 (95% CI 0.5-12.4). The odds of poor vision with broken FAZ was 2.5 (95% CI,0.61-3.64). Eighteen eyes had both broken FAZ and broken IS-OS junction. Odds of having poor vision with broken FAZ and broken IS-OS junction were 2.5. The duration of diabetes (>9 years) had a significant correlation with a disrupted IS-OS junction (p=0.004). Mean BCVA of the study group was 0.4 logMAR and in controls 0.1 respectively. Mean BCVA in the patients with disrupted IS-OS was 0.5 logMAR and intact IS-OS was 0.2 logMAR respectively.

Status of FAZ and IS-OS junction	N	Visual Acuity	Percentage of eyes with good vision
Broken FAZ Broken IS-OS	18	3/18 eyes had 0.0 logMAR (Snellen equivalent 6/6 or 20/20)	16.66
Broken FAZ Intact IS-OS	12	5/12 eyes had 0.0 logMAR (Snellen equivalent 6/6 or 20/20)	41.66

Table 1: FAZ and IS-OS junction with visual acuity.

The positive predictive value (PPV) of disrupted IS-OS junction in broken FAZ was 47.37% (range 30.98% to 64.18%) and the negative predictive value (NPV) of intact IS-OS junction in broken FAZ was 50% (range 29.12% to 70.88%). The PPV in diabetes age of 9 years or longer was 100% (range 81.47% to 100%) and the NPV was 71.43% (range 55.42% to 84.28%). The combined PPV of poor vision (<20/30) and longer diabetes duration (>9 years) was 88.89% (range 51.75% to 99.72%) and the NPV was 100% (range 71.51% to 100%) (Table 2: Relationship of Positive Predictive Value (PPV) and Negative Predictive Value (NPV) with Diabetic age and poor vision).

	PPV	NPV
Diabetic age of 9 years or more	100% (range 81.47% to 100%)	71.43% (range 55.42% to 84.28%)
Poor vision longer diabetes duration	88.89% (range 51.75% to 99.72)	100% (range 71.51% to 100%)

Table 2: Statistical results of diabetic age and poor vision.

All 32 eyes in the control group had intact FAZ with clear distinguishable IS-OS margin (Figure 1). The macula was thickened in 8 eyes. The eyes with thicker macula had poorer vision, but there was no linear correlation. Examples of broken FAZ

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and corresponding IS-OS junction are shown in Figure 2.

Discussion

Macular blood supply is processed by three capillary plexuses, the superficial capillary plexus (SCP) that lies in the retinal nerve fiber layer, the middle capillary plexus (MCP) that lies in the inner border of the inner nuclear layer, and the deep capillary plexus (DCP) that lies in the outer border of the inner nuclear layer. Broken FAZ results from the dysfunction of DCP and MCP [6,7]. Although FFA can only reflect the status of SCP but Reznicek et al suggested this could lead disturbance in hemodynamic equilibrium that weakens the capillary bed surrounding the FAZ that could also be due to the involvement of DCP and MCP [8-12]. This leads to hypoxia at the FAZ [9]. Hypoxic changes are the reason for the enlargement of the FAZ and simultaneously cause diabetic macular edema. FAZ enlargement leads to damage of the inner and outer retinal layers that involves disruption of photoreceptors, and external limiting membrane [10]. Because the outer (supplied by choroid) and the retinal blood supply are affected, it is reasonable to expect the disturbance in the inner and outer retinal segments, manifested in the IS-OS junction defect in the OCT. The most measurable functional effect is reduction of visual acuity in presence of both broken FAZ and distorted IS-OS junction. However, this is good to also look for the choroidal thickness but due to poor delineated margin we could not be able to understand the choroidal sclera interface.

This study looked at a possible relation between the distorted avascular zone at the fovea and the disrupted photoreceptor line at the zone of ischemia. In this study 60% of eyes had both broken FAZ and disrupted IS-OS junction, and 40% of eyes did not have. Thus, the positive predictive value (PPV) of IS-OS junction disruption in broken FAZ was 47.37% (range 30.98% to 64.18%) and the negative predictive value (NPV) of intact IS-OS junction in broken FAZ was 50% (range 29.12% to 70.88%).

The anatomy of the IS-OS junction is influenced by the state of the FAZ. The physical changes in the outer and inner segmental changes in the OCT could manifest either as 'absent' or 'faint' IS-OS junction. An absent IS-OS junction at the point of broken FAZ directly correlates with the amount of ischemia and could be secondary to photoreceptor damage [11]. Faint IS-OS line or hypo reflective margin of photoreceptor at the area of distortion possibly highlight the early degeneration of the cone outer segment tip (COST) as well as the surrounding photoreceptor cells. Reznicek L and his co-workers mentioned the ischemia of the deep and mid capillary plexuses cause IS-OS junction disruption [12]. But a cystic fovea in a diabetic maculopathy is likely to alter light transmission to the extent of the appearance of the IS-OS junction disruption [13,14].

In this study we found that a broken IS-OS junction manifests in a poor visual acuity (18 of 30 eyes; 60% had both broken FAZ and disrupted IS-OS junction) and is possibly correlates with increasing diabetic age (diabetic age: 9.42+3.15 years in broken IS-OS group and 3.58+0.6 years in intact IS-OS group; p=0.004), but not with the macular thickness. Thus, a broken IS-OS junction could possibly estimate the visual acuity and diabetic age in a patient with broken

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FAZ. Early ischemic changes may also lead to neuro degeneration and therefore causes sub clinical changes also at the inner retina [15,16]. However, we did not evaluate the choroidal contribution in this study, but it is obvious that perifoveal blood supply is maintained by choriocapillaries and impact to the vasculature may lead to photoreceptor disruption as well as broken FAZ.

The weakness of the study is the small sample size. We understand that the OCT angiography (OCTA) is a new non- invasive imaging technology that helps outline the FAZ at different levels of the retinal layers [17]. OCTA could be alternate measures of FFA, though it is expensive, not yet widely available and has few certain disadvantages. The strength of this study is the correlation of the IS-OS junction with the visual acuity. This study suggests that a distorted or faint OCT could indicate a grossly or mildly broken FAZ in absence of actual angiogram and predict a relatively poor vision.

Conclusion

Disrupted IS-OS junction on OCT could indicate an ischemic macula, but correlation with visual acuity is important to intensify this feature.

Conflicts of Interest

None.

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