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Evaluation of Peripheral Retinal Leakage by Ultra-Widefield Fluorescein Angiography in Patients with Non proliferative Diabetic Retinopathy

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Abstract: Nonproliferative diabetic retinopathy (NPDR) is characterised by progressive microvascular damage that may extend beyond the posterior pole, where conventional imaging often fails to detect early peripheral ischemia and leakage. **Objective:** To evaluate peripheral retinal leakage using ultra-widefield fluorescein angiography and determine its association with clinical severity, angiographic abnormalities, and treatment outcomes in patients with NPDR. **Methodology:** This was a hospital-based cross-sectional analytical study conducted at Bakhtawar Amin Hospital, Multan from August 2024 to August 2025 including 355 patients diagnosed with nonproliferative diabetic retinopathy (NPDR). **Results:** Peripheral retinal leakage was detected in 213 patients (60%). The leakage group was older (58.4 ± 9.8 vs 55.9 ± 10.2 years, p = 0.032) and had longer diabetes duration (12.6 ± 5.1 vs 9.2 ± 4.7 years, p = 0.001). Moderate-to-severe NPDR was more frequent among patients with leakage (74.2% vs 38.7%, p = 0.001), along with higher rates of diabetic macular edema (50.2% vs 14.8%). Angiographic abnormalities were significantly greater in the leakage group, including capillary nonperfusion (78.4% vs 21.8%), peripheral ischemic index >10% (69.9% vs 12.7%), microaneurysm clusters (86.4% vs 42.3%), and vascular staining (51.2% vs 14.1%) (all p = 0.001). These patients also required more frequent laser therapy (43.2% vs 13.4%) and anti-VEGF treatment (41.3% vs 12.0%), with a lower rate of visual improvement at follow-up (63.8% vs 81.0%). **Conclusion:** Peripheral retinal leakage is common in NPDR and is strongly associated with greater ischemic burden, higher disease severity, increased treatment requirements, and poorer visual outcomes. Ultra-widefield fluorescein angiography provides valuable additional information for comprehensive evaluation and risk stratification in patients with diabetic retinopathy.

Keywords: diabetic retinopathy, nonproliferative diabetic retinopathy, ultra-widefield fluorescein angiography

INTRODUCTION

Diabetic retinopathy (DR) is a major cause of amenable visual loss among working-age adults worldwide and is driven by microvascular damage resulting from chronic hyperglycemia, leading to capillary leakage, ischemia, and retinal dysfunction [1]. As diabetes is becoming more common in the world, it has become vital to detect the subtly altering vascular retinal formation in its early stages in order to avoid vision-threatening complications [3]. The first stage of the disease is termed nonproliferative diabetic retinopathy (NPDR), which is typically characterised by microaneurysms, haemorrhages, and intraretinal microvascular abnormalities, but can involve significant pathology extending beyond the posterior pole and may not be clinically apparent [5]. Traditional fundus photography techniques and standard fluorescein angiography examine only the central area and provide limited retinal coverage, which may miss peripheral ischemia and leakage that also play important roles in disease progression [7]. There is mounting evidence that untreated peripheral nonperfusion facilitates the release of angiogenic and inflammatory mediators, thereby enhancing vascular permeability and accelerating the development of diabetic macular oedema and proliferative changes [9].

Therefore, relying on the posterior pole alone may not provide an accurate assessment of NPDR severity. Ultra-widefield fluorescein angiography (UWFA) has become a superior form of imaging that can capture a wide view of the retina, which is approximately 200 degrees, into a single image, enabling the thorough examination of the peripheral retinal circle of blood vessels [11]. Such a broader visualisation helps identify peripheral capillary dropout, microvascular defects, and leakage patterns that cannot be detected by traditional imaging methods [13]. It has been suggested that peripheral leakage abnormalities detected on UWFA are a sign of active disease and may be associated with higher retinopathy grades and an increased risk of complications [15]. Besides, the assessment of the level of peripheral leakage can enhance the risk stratification and inform the management choices including closer monitoring or a more timely intervention [2]. Past studies have established that wider-field angiography identifies larger ischemic regions as opposed to routine procedures, thus offer a more precise picture of the retinal involvement [16].-tissue lesions.

Objective:

To evaluate peripheral retinal leakage using ultra-widefield fluorescein angiography and determine its association with clinical severity, angiographic abnormalities, and treatment outcomes in patients with NPDR.

METHODOLOGY

This was a hospital-based cross-sectional analytical study conducted at Bakhtawar Amin Hospital, Multan from August 2024 to August 2025 including 355 patients diagnosed with nonproliferative diabetic retinopathy (NPDR). Patients of either gender aged 18 years and above with a confirmed diagnosis of type 1 or type 2 diabetes mellitus were eligible for inclusion in the study. Only those with clinically confirmed nonproliferative diabetic retinopathy on fundus examination were enrolled. Participants were required to be willing to undergo fluorescein angiography and to provide informed written consent prior to participation. Patients with proliferative diabetic retinopathy were excluded from the study. Additional exclusion criteria included a history of retinal laser photocoagulation or intraocular surgery within the past six months, presence of media opacities that interfered with adequate fundus visualisation, and any history of retinal vascular occlusion or other coexisting retinal diseases.

Data collection

Data were collected using a structured proforma. Demographic variables included age, gender, and duration of diabetes. Clinical information, including best-corrected visual acuity, systemic comorbidities, and NPDR stage, was documented. All participants underwent a comprehensive ophthalmic examination including visual acuity assessment, slit-lamp biomicroscopy, intraocular pressure measurement, and dilated fundus evaluation. Ultra-widefield fluorescein angiography was performed using a widefield retinal imaging system capable of capturing approximately 200 degrees of the retina in a single image. Following intravenous administration of fluorescein dye, sequential angiographic images were obtained to evaluate peripheral retinal vasculature. Parameters assessed included peripheral retinal leakage, areas of capillary nonperfusion, microaneurysms, and other vascular abnormalities. Peripheral leakage was recorded as present or absent and graded according to its extent and distribution. All images were interpreted by experienced ophthalmologists using uniform criteria to maintain consistency and reduce observer bias.

Statistical analysis

Data were entered and analyzed using SPSS version 25.0. Continuous variables such as age and duration of diabetes were expressed as mean ± standard deviation, while categorical variables were summarized as frequencies and percentages. Associations between peripheral leakage and severity of NPDR were evaluated using the chi-square test or appropriate statistical tests. A p-value of ≤ 0.05 was

considered statistically significant.

RESULTS

Among the 355 participants, peripheral retinal leakage was identified in 213 patients (60.0%), while 142 (40.0%) showed no leakage. Patients with leakage were slightly older, with a mean age of 58.4 ± 9.8 years compared with 55.9 ± 10.2 years in those without leakage (p = 0.032). Male predominance was observed in both groups (57.3% vs 49.3%), although gender distribution was not statistically significant (p = 0.150). The leakage group had a longer duration of diabetes (12.6 ± 5.1 vs 9.2 ± 4.7 years, p = 0.001) and a higher prevalence of hypertension (68.5% vs 51.4%, p = 0.002).

Table 1. Comparison of Baseline Demographic and Clinical Characteristics Between Leakage Groups

Variable	Category	Leakage Present (n=213)	Leakage Absent (n=142)	Total (n=355)	p-value
Age (years)	Mean ± SD	58.4 ± 9.8	55.9 ± 10.2	57.4 ± 10.0	0.032
Gender	Male	122 (57.3)	70 (49.3)	192 (54.1)	0.150
	Female	91 (42.7)	72 (50.7)	163 (45.9)	0.150
Duration of diabetes	Mean ± SD (years)	12.6 ± 5.1	9.2 ± 4.7	11.2 ± 5.3	0.001
Hypertension	Present	146 (68.5)	73 (51.4)	219 (61.7)	0.002
	Absent	67 (31.5)	69 (48.6)	136 (38.3)	0.002

Only 25.8% of patients with leakage had mild NPDR compared with 61.3% in the non-leakage group, whereas moderate (48.8%) and severe NPDR (25.4%) were considerably more common among those with leakage (p = 0.001). Visual acuity was also poorer in the leakage group, with fewer patients maintaining vision ≥6/12 (50.7% vs 76.1%) and more patients exhibiting moderate or severe impairment (49.3% vs 23.9%). Diabetic macular edema was markedly higher in patients with leakage (50.2% vs 14.8%, p = 0.001).

Table 2. Comparison of NPDR Severity and Visual Outcomes Between Leakage Groups

Variable	Category	Leakage Present (n=213)	Leakage Absent (n=142)	Total (n=355)	p-value
NPDR severity	Mild	55 (25.8)	87 (61.3)	142 (40.0)	0.001
	Moderate	104 (48.8)	47 (33.1)	151 (42.5)	0.001
	Severe	54 (25.4)	8 (5.6)	62 (17.5)	0.001
Visual acuity	≥6/12	108 (50.7)	108 (76.1)	216 (60.8)	0.001
	6/18–6/60	82 (38.5)	26 (18.3)	108 (30.4)	0.001
	<6/60	23 (10.8)	8 (5.6)	31 (8.7)	0.001
Diabetic macular edema	Present	107 (50.2)	21 (14.8)	128 (36.1)	0.001
	Absent	106 (49.8)	121 (85.2)	227 (63.9)	0.001

Capillary nonperfusion was present in 78.4% of leakage cases compared with only 21.8% without leakage (p = 0.001). A peripheral ischemic index greater than 10% was observed in 69.9% versus 12.7%, respectively. Microaneurysm clusters were detected in 86.4% of leakage cases compared with 42.3% of non-leakage eyes, while vascular staining was also more frequent (51.2% vs 14.1%).

Table 3. Comparison of Ultra-Widefield Angiographic Parameters Between Leakage Groups

Variable	Category	Leakage Present (n=213)	Leakage Absent (n=142)	Total (n=355)	p-value
Capillary nonperfusion	Present	167 (78.4)	31 (21.8)	198 (55.8)	0.001
	Absent	46 (21.6)	111 (78.2)	157 (44.2)	0.001
Peripheral ischemic index >10%	Present	149 (69.9)	18 (12.7)	167 (47.0)	0.001
	Absent	64 (30.1)	124 (87.3)	188 (53.0)	0.001
Microaneurysm clusters	Present	184 (86.4)	60 (42.3)	244 (68.7)	0.001
	Absent	29 (13.6)	82 (57.7)	111 (31.3)	0.001
Vascular staining	Present	109 (51.2)	20 (14.1)	129 (36.3)	0.001
	Absent	104 (48.8)	122 (85.9)	226 (63.7)	0.001

Nearly half of patients with leakage required laser photocoagulation (43.2%) compared with only 13.4% without leakage (p = 0.001), and anti-VEGF therapy was required in 41.3% versus 12.0%, respectively. Visual improvement at follow-up was lower in the leakage group (63.8% vs 81.0%), with a higher proportion showing no improvement (36.2% vs 19.0%, p = 0.002).

Table 4. Comparison of Clinical Outcomes and Treatment Requirement Between Leakage Groups

Variable	Category	Leakage Present (n=213)	Leakage Absent (n=142)	Total (n=355)	p-value
Required laser therapy	Yes	92 (43.2)	19 (13.4)	111 (31.3)	0.001
	No	121 (56.8)	123 (86.6)	244 (68.7)	0.001
Required anti-VEGF	Yes	88 (41.3)	17 (12.0)	105 (29.6)	0.001
	No	125 (58.7)	125 (88.0)	250 (70.4)	0.001
Visual improvement at follow-up	Improved	136 (63.8)	115 (81.0)	251 (70.7)	0.002
	No improvement	77 (36.2)	27 (19.0)	104 (29.3)	0.002

DISCUSSION

This paper assessed the peripheral retinal leakage with ultra-wide field fluorescein angiography in 355 nonproliferative diabetic retinopathy cases and proved the leakage is prevalent and clinically significant. It was found that 213 patients (60% of all patients with NPDR) had peripheral leakage, indicating that, rather than being apparent on standard posterior pole check-up, over half of patients with peripheral vascular pathology harbour active peripheral leakage. The frequency of peripheral leakage is also similar to that observed in other studies, in which wide-field imaging revealed a significantly higher disease burden than conventional angiography [17]. Baseline variables indicated that patients with leakage were a little older (58.4 ± 9.8 vs 55.9 ± 10.2 years), had a greater duration of diabetes (12.6 ± 5.1 vs 9.2 ± 4.7 years), and were more likely to have hypertension (68.5% vs 51.4%), indicating that chronic metabolic and systemic vascular stress is one cause of peripheral ischemic alterations. Such trends are consistent with prior studies that have found longer disease duration and systemic comorbidities to be significant predictors of retinopathy progression [18]. There was a good correlation between leakage and severity of NPDR. Within the non-leakage group, mild NPDR was the most common (61.3%), whereas moderate (48.8%) and severe NPDR were observed in patients with leakage. There was also an improved visual function with less eyes having ≥ 6/12 vision (50.7% vs 76.1%), increased visual impairment and diabetic retinopathy (50.2% vs 14.8%). These results indicate that leakage is an indicator of severe microvascular damage and impaired function. Similar correlations between peripheral ischemia and the increasing retinopathy grades had been reported in earlier studies [19].

Angiographic examination also demonstrated leakage and extensive peripheral pathology. The presence of capillary nonperfusion in the cases of leakages was 78.4% and 21.8% in the cases of absence of leakages with a peripheral ischemic index exceeding 10% (69.9% and 12.7% respectively). Microaneurysm clusters were also significantly increased (86.4% vs 42.3%), as well as vascular staining (51.2% vs 14.1%). These findings indicate that the leakage is not a single outcome but a component of a larger process of ischemic and inflammatory retinal pathology of the peripheral area. The same patterns of extensive cases of nonperfusion that are in association with leakage have been experienced in past studies which reiterate the importance of nonperfusion as a disease activity indicator [20]. Patients with leakage required more intensive clinical management, with more receiving laser therapy (43.2% vs 13.4%) and anti-VEGF injections (41.3% vs 12.0%). The visual improvement at follow up was also less (63.8 vs 81.0), which means that it has a worse prognosis. The implications of these observations are that peripheral leakage identifies a subgroup of disease that is more active and requires treatment. Similar studies have been done in the past and they have revealed higher rates of intervention and worse outcomes in eyes with large peripheral vascular abnormalities [21]. This study was limited by its single-center design, cross-sectional methodology, absence of longitudinal progression data, and reliance on fluorescein angiography without adjunctive quantitative imaging or functional biomarkers, which may restrict generalizability and limit assessment of long-term prognostic impact of peripheral leakage.

CONCLUSION

It is concluded that peripheral retinal leakage detected on ultra-widefield fluorescein angiography was present in a substantial proportion of patients with NPDR (60%) and showed strong associations with longer diabetes duration (12.6 vs 9.2 years), higher rates of moderate-to-severe disease (74.2%), increased macular edema (50.2%), greater ischemic burden including capillary nonperfusion (78.4%), and higher treatment requirements for laser or anti-

VEGF therapy; therefore, ultra-widefield imaging serves as a valuable adjunct for comprehensive evaluation, risk stratification, and early identification of patients at greater risk of progression and visual deterioration.

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