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Predominant peripheral lesions in patients with diabetic retinopathy and its association with systemic comorbidities

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Purpose: To determine the associations of predominant peripheral lesions (PPLs) with systemic comorbidities in individuals with diabetic retinopathy. **Methods:** This is a multicenter cross-sectional observational study conducted across three tertiary eye care centers in south India between January 2019 and July 2021. Ultra-widefield fundus images of consecutive patients with varying severity of diabetic retinopathy with data on systemic comorbidities were classified based on the presence or absence of PPL. Systemic comorbidities (hypertension, diabetic kidney disease, coronary artery disease, dyslipidemia, and anemia) were compared between the two groups. **Results:** A total of 879 participants (70.1% males) were included in the study, of which 443 (50.4%) patients had PPL. The mean age of the study participants was 56 ± 10 years, mean age of onset of diabetes was 41.24 ± 11.6 years, and mean duration of diabetes was 15.39 ± 7.6 years. The number of PPL increased with increasing severity of DR. Of all the systemic comorbidities analyzed, we found that coronary artery disease (CAD) had a significant association with PPL (Odds ratio [OR]-1.69; 95% confidence interval [CI], 1.12–2.55; P = 0.013) after adjusting for diabetic retinopathy severity, duration of diabetes, and age of onset of diabetes. **Conclusion:** The presence of PPL is a marker for coronary artery disease and early referral to cardiology is warranted.

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Retinal imaging has evolved significantly over the past 2 decades. Traditionally, fundus cameras that captured retinal images were limited to 33 to 50 degrees of the posterior pole, covering approximately 30% of the retinal surface area.[1,2] In contrast, more recent transition to ultra-widefield (UWF) imaging allows visualization of more than 80% of the retina, enabling a better appreciation of the retinal periphery and peripheral lesions.[1,2] Diabetic retinopathy (DR) is prevalent in a third of people with diabetes (PwD). Predominantly peripheral lesions (PPLs) are defined as any hemorrhages, microaneurysms, venous beading, intraretinal microvascular anomalies (IRMA), or retinal neovascularization elsewhere (NVE) that are present predominantly in any peripheral field in eyes with DR.[2]

Diabetes is a multisystem disorder that can result in both microvascular and macrovascular complications. After 20 years of having diabetes, 99% of people with type 1 diabetes and about 60% of individuals with type 2 diabetes will develop DR.[3] Other diabetic complications include diabetic kidney disease, cardiovascular abnormalities, and peripheral neuropathy.[3] In addition, most PwD also suffer from hypertension (HT). These comorbidities can occur with or without DR. In eyes with DR, these comorbidities can occur with any severity level of DR.[3-5]

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A recent systematic review, highlighted the need for improved multispeciality care for PwD due to the associations with these comorbidities. Although referring every person to DR for medical evaluation is an ideal scenario, it is challenging to do so in clinical practice. Better stratification of patients with DR at high risk of comorbidities may help in the implementation of feasible multispecialty pathways.[6] In this study, we aimed to characterize the DR lesions further to evaluate whether PPL may be used as a marker of any systemic comorbidities.

Methods

This multicenter cross-sectional observational study on anonymized data and images was conducted in three tertiary eye care centers in south India and the subjects were enrolled between January 2019 and July 2021. The study adhered to the tenets of the Declaration of Helsinki for research involving human subjects and was approved by the Institutional Review Boards at each institution.

Patients

Treatment naive patients with DR with type 1 or type 2 diabetes with gradable UWF retinal images and available data on systemic comorbidities were included in the study. Eligible

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patients were identified from the retinal imaging database and electronic medical records. Exclusion criteria included incomplete records on systemic comorbidities or retinal images that were blurred or had artifacts that did not allow visualization of all retinal fields.

Data

Systemic data collected included the presence or absence of hypertension, history of stroke, coronary artery disease (CAD), or chronic kidney disease (CKD).

Definitions

Hypertension was diagnosed if the subjects were on treatment for high blood pressure (BP) or if systolic BP was ≥140 and/or diastolic BP was ≥90 mmHg.[7]

Stroke was diagnosed if the patient had paresis or plegia with records confirming neurological deficit due to stroke.[8]

CKD was diagnosed if subjects had a history of chronic kidney disease, dialysis, or Estimated Glomerular filtration rate (eGFR) records of <60 mL/min[9] and CAD was diagnosed if the patient had a positive medical history of myocardial infarction or history of bypass surgery or angioplasty.

Recent blood investigation reports collected included HbA1c, hemoglobin, and serum cholesterol. Controlled diabetes was defined as HbA1c of <7%. Anemia was present, if hemoglobin level was less than 13 gm% in males and less than 12 gm% in females, and hypercholesterolemia was diagnosed if serum cholesterol value was more than 200 mg/dL. Details about the systemic conditions were extracted from valid documents available with the patients.

Retinal imaging

Retinal images captured on UWF imaging (Optos Daytona plus [Optos Ltd. Dunfermline, Scotland]) by trained technicians after mydriasis were adjusted for brightness and contrast on a desktop monitor.

Analysis of the ultra-widefield retinal images

The UWF images were graded by trained investigators. A single fovea-centered gradable image involving all fields was used for analysis. The Early Treatment Diabetic Retinopathy Study (ETDRS) grid available in Optos software was projected on the image for determining the boundaries of each field. The peripheral field was divided into extended field 3 to field 7 [Fig. 1] Field 1 is centered on the optic nerve and field 2 is centered on the macula. Extended Field 3 (EF3) was defined as the area of the retina temporal to the macula. The superior and inferior limits of EF3 were defined by horizontal lines at the uppermost and lowermost positions of the superior and inferior temporal vascular arcades, respectively. A vertical line through the center of the optic disc limited by the lines at the superior and inferior vascular arcades was defined as EF4 (superior temporal) and EF5 (inferior temporal), respectively. A horizontal line across the center of the macula and a vertical line across the center of the optic disc were defined as EF6 (superior nasal) and EF7 (inferior nasal).

Each UWF image was evaluated for the presence of dot and blot hemorrhages/microaneurysms, venous beading, IRMA, and NVE. Each image was given a DR severity level based on the lesions within the ETDRS grid using the International Clinical Diabetic Retinopathy Classification.[10] The DR severity scale divides diabetic retinopathy into five grades: no retinopathy, mild nonproliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, or proliferative diabetic retinopathy (PDR). Each lesion was then defined as predominantly peripheral in that particular field if more than 50% of the lesion being graded was present in the retinal peripheral field when compared with the ETDRS field [Fig. 2].[2] Each patient was considered to have PPL if at least one of the peripheral fields in either one or both the eyes had predominant diabetic lesions compared with the ETDRS grid.

Statistical analysis

The data were entered in Microsoft Excel spreadsheet. A descriptive analysis of the population's characteristics was carried out. Results of continuous variables are reported as mean and standard deviation (SD) and that of categorical variables are reported as counts and percentages. The differences between quantitative variables were analyzed using Mann–Whitney *U* test. Odds ratio (OR) and 95% confidence interval (CI) were measured. Logistic regression analysis was done to determine independent determinants of PPL. Chi-square test and Fisher's exact test were used to find the difference between the categorical variables. *Z* test was used to find the difference in the two proportions. *P* value <0.05 is considered significant for all the comparisons.

Data were analyzed using IBM SPSS 26.0 Version.

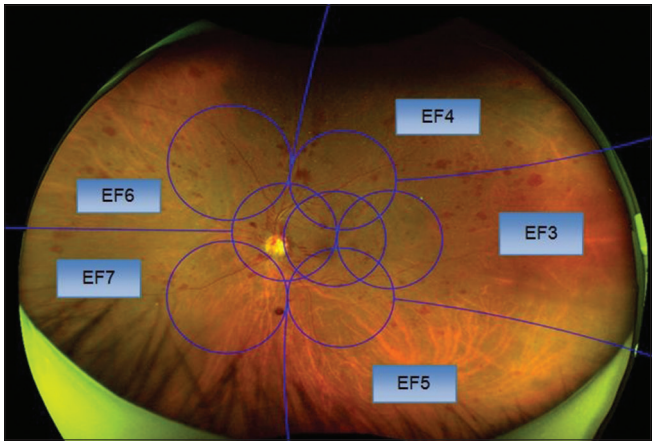

Figure 1: Ultra-widefield image with ETDRS grid

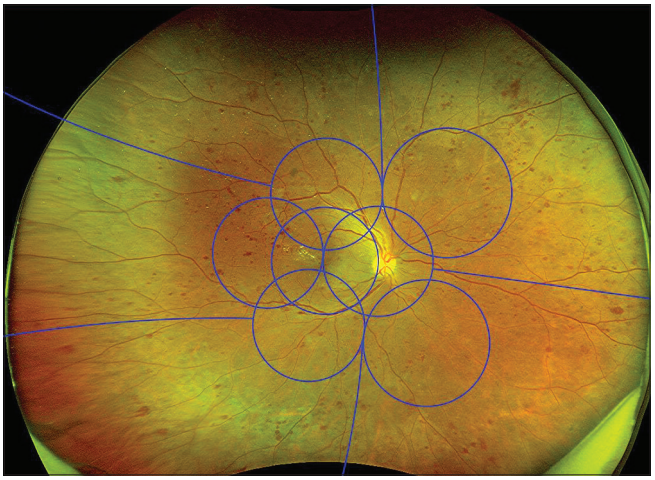

Figure 2: Ultra-widefield image showing predominant peripheral lesions

Results

The data from 950 eligible patients from three tertiary eye care centers in south India were evaluated in this study. Out of these, 71 patients had ungradable retinal images and hence were excluded from the study. Table 1 gives the baseline characteristics of the study population. Baseline DR severity in the study population based on the ETDRS grid was no DR in 1.9%, mild NPDR in 26.8%, moderate NPDR in 20.8%, severe NPDR in 23.1%, and PDR in 27.3%. Table 2 shows a comparison of baseline diabetic characteristics in patients with and without PPL.

A total of 443 (50.4%) patients had PPL in at least one of the peripheral fields. Hemorrhages/microaneurysms (84.9%) were the most frequently observed PPL. For each DR grade, the distribution of PPL is given in Fig. 3. Prevalence of PPL was higher among subjects with PDR (75.4%). Interestingly, 11.8% of patients with no DR within the ETDRS grid showed PPL. PPL prevalence was 18.6% in those patients with mild NPDR, 61.7% in moderate NPDR, 50.7% in severe NPDR, and 75.4% in PDR. Prevalence of PPL increased significantly with worsening severity of DR. (OR-3.16; 95% CI, 2.39–4.18, $P = 0.001$).

The mean duration of diabetes and age of onset of diabetes were similar in patients with and without PPL. The prevalence of PPL increased with the duration of diabetes. Prevalence of PPL was more in individuals with more than 5 years of diagnosed diabetes (OR = 2.14; 95% CI, 1.24–3.69; $P = 0.006$). Older age of onset of diabetes was found to be protective for the presence of PPL. Patients who developed diabetes after 40 years were found to have a lesser chance of PPL. (OR = 0.72; 95% CI, 1.54–0.95; $P = 0.022$), but their mean duration of diabetes was 12.63 ± 6.36 years and statistically less than those aged 40 years or below ($P = 0.001$). There was no statistically significant association between type of diabetes and PPL, with 42.47% of type 1 diabetes patients and 51.19% of type 2 diabetes having PPL.

Table 3 shows the association of various systemic comorbidities with PPL, and CAD was found to be significantly associated with PPL. Multiple logistic regression was done with PPL as the dependent variable and various factors associated with PPL as the independent variable. Table 4 shows that after adjusting for severity of diabetic retinopathy, age of onset of diabetes, and duration of diabetes, CAD was significantly associated with presence of PPL (OR-1.69; 95% CI, 1.12–2.55; $P = 0.013$). Prevalence of CAD in our study population was 13.8%. Association of different peripheral DR lesions was done, which revealed that PPL hemorrhages/microaneurysms (OR = 1.91 95% CI, 1.30–2.81; $P = 0.001$) had a significant association with CAD.

Table 1: Baseline characteristics of study population

No. of patients	879
Sex, *n* (%)	
Female	263 (29.9)
Male	616 (70.07)
Age (in years), Mean (SD)	56.66 (10.50)
Duration of diabetes (in years), Mean (SD)	15.39 (7.69)
Age of onset of diabetes (in years), Mean (SD)	41.24 (11.60)
Type 1 diabetes, *n* (%)	74 (8.41)
Type 2 diabetes, *n* (%)	805 (91.58)
No DR, *n* (%)	17 (1.93)
Mild NPDR, *n* (%)	236 (26.84)
Moderate NPDR, *n* (%)	183 (20.81)
Severe NPDR, *n* (%)	203 (23.09)
PDR, *n* (%)	240 (27.30)
HbA1c > 7%, *n* (%)	493 (56.08)
Hypertension, *n* (%)	398 (45.27)
Diabetic kidney disease, *n* (%)	123 (13.99)
Coronary artery disease, *n* (%)	122 (13.87)
Hypercholesterolemia, *n* (%)	127 (14.44)
Anemia, *n* (%)	150 (17.06)
Stroke, *n* (%)	36 (4.09)

NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; HbA1C, glycated hemoglobin

Table 2: Comparison of diabetes characteristics in patients with and without PPL

	n	Mean (SD)	*P*
Duration of diabetes in years			
PPL	441	15.84 (7.23)	0.031
No PPL	434	14.94 (8.10)	
Age of onset of diabetes in years			
PPL	441	40.70 (10.49)	0.023
No PPL	434	41.79 (12.62)	
HbA1c			
PPL	269	9.03 (1.93)	
No PPL	315	8.92 (1.90)	0.376

PPL, predominantly peripheral lesions; HbA1C, glycated hemoglobin

Discussion

Our study results show that frequency of PPL increases with severity of DR, duration of diabetes, early onset of diabetes, and history of coronary artery disease. Previous studies have shown that presence of PPL increases the risk of DR progression over 4 years by 3.2-fold and PPL may suggest a more severe level of DR at 10%.[2,11] Our study also shows the prevalence of PPL is 50% when all severity levels of DR are considered, with 11.8% of eyes with no DR demonstrating PPL highlighting that UWF imaging may alter the severity level of DR when

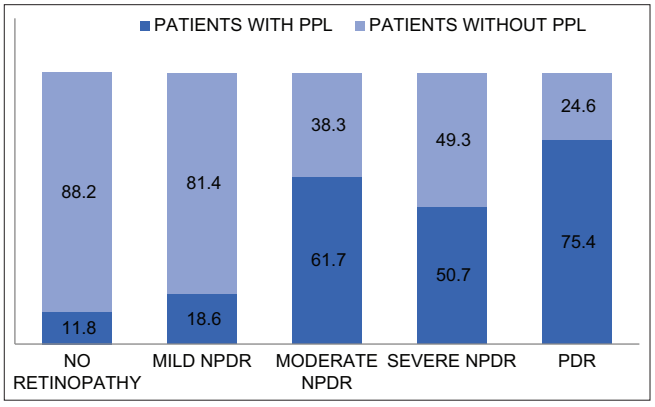

Figure 3: Prevalence of predominant peripheral diabetic retinopathy lesions in different grades of diabetic retinopathy

compared with that recorded within the ETDRS grid. The PPL rates are high in clinic-based studies.[4,12] Based on our study results, we estimate that the prevalence of PPL at population level in people with diabetes is around 18%.

We show a high prevalence of CAD in patients with PPL. Therefore PPL may serve as a marker for early detection of cardiovascular disease. Association between DR of various grades and CAD is established.[4,13,14] Chennai Urban Rural Epidemiology Study (CURES) eye study 3 reported a significant association between CAD and DR in a south Indian population.[15] Similarly, a study in a Chinese population also showed the association of DR with asymptomatic obstructive CAD.[16] Poor long-term surgical outcome of CAD has been reported in Japanese patients with DR.[17] A meta-analysis by Kramer *et al*.[18] confirmed that the presence of DR increases the risk of mortality and cardiovascular events in both type 1 and type 2 diabetes. Our study adds value as it further stratifies the risk of CAD in patients with DR based on PPL.

Predominance of peripheral lesions in patients with CAD may be attributed to more endothelial changes in the peripheral retinal vasculature. Changes in retinal microvasculature may reflect microvascular changes in the rest of the systemic vascular system as the relation between the microvascular and macrovascular diseases remains poorly understood.

Previous studies have also shown an association between microvascular retinal abnormalities with stroke.[19,20] When each lesion type is associated with systemic comorbidities, it has been reported that retinal microaneurysms and hemorrhages are seen more in patients with stroke while retinal arteriolar changes are more prevalent in ischemic heart disease.[15] Our study did not show a significant association of PPL with stroke. The prevalence of stroke in our population was low. Selection bias cannot be ruled out as this is a clinic-based study.

Studies have documented that earlier onset of diabetes may cause an increase in severity and prevalence of DR; this is consistent with our data where age of onset of diabetes was found to be protective for the presence of PPL.[21] Patients with onset of diabetes after the age of 40 years had a lesser prevalence of PPL. Association between PPL and diabetic severity has already been reported in prior studies.[4,6,22]

The main strength of this study is it is the first study, to the best of our knowledge, that reports the association between PPL and systemic comorbidities in people with diabetes. This is a multicenter study with a large sample size of individuals with varying grades of severity of DR who had undergone UWF imaging along with systemic, clinical, and biochemical assessment. This study highlights the importance of evaluation of peripheral retina in all diabetic patients during routine screening. It emphasizes the need to specifically look for peripheral lesions in diabetic patients and to advise a cardiology workup in patients with PPL mainly hemorrhages.

Table 3: Association of systemic comorbidities with PPL

Systemic comorbidity	No. of patients without PPL *n* (%)	No. of patients with PPL *n* (%)	*P*
CKD (*n*=123)			
Present	53 (43.1)	70 (56.9)	0.113
Absent	383 (50.8)	371 (49.2)	
CAD (*n*=122)			
Present	47 (38.5)	75 (61.5)	0.013
Absent	389 (51.5)	366 (48.5)	
HTN (*n*=398)			
Present	188 (47.2)	210 (52.8)	0.181
Absent	248 (51.8)	231 (48.2)	
Stroke (*n*=36)			
Present	14 (38.9)	22 (61.1)	0.185
Absent	422 (50.2)	419 (49.8)	
Anemia (*n*=150)			
Present	78 (52.0)	72 (48.0)	0.052
Absent	87 (41.6)	122 (58.4)	
Hypercholesterolemia (*n*=127)			
Present	57 (44.9)	70 (55.1)	0.934
Absent	132 (44.4)	165 (55.6)	
HbA1C			
<7	39 (42.85)	52 (57.14)	0.504
>7	230 (46.65)	263 (53.34)	

CAD, coronary artery disease; CKD, chronic kidney disease; HbA1C, glycated hemoglobin

Table 4: Multiple logistic regression showing associations of PPL

Independent variables	Patients with PPL *n* (%)	Patients without PPL *n* (%)	OR (95% CI)	*P*
CAD				
Yes	75 (61.5)	47 (38.5)	1.686 (1.12-2.55)	0.013
No	366 (48.5)	389 (51.5)		
Age of onset of diabetes				
>40	213 (45.7)	253 (54.3)	0.72 (0.54-0.95)	0.022
≤40	228 (55.7)	181 (44.3)		
DR severity				
Mild and moderate NPDR	284 (64.1)	159 (35.9)	3.16 (2.39-4.18)	0.001
Severe NPDR and PDR	159 (36.5)	277 (63.5)		
Duration of diabetes				
>5	418 (52.1)	385 (47.9)	2.14 (1.24-3.69)	0.006
≤5	23 (31.9)	49 (68.1)		

CAD, coronary artery disease; DR, diabetic retinopathy; PPL, predominantly peripheral lesions

However, this is a retrospective study of patients in secondary care where the data has been extracted from available electronic medical records so further studies are required to confirm our findings at a population level. Moreover, as it is a cross-sectional study, causal inferences cannot be drawn.

Conclusion

Our study shows an association between CAD and PPL and hence PwD with PPL, irrespective of DR severity level, needs to have regular cardiology workup for early detection and timely management of CAD.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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