

Propensity for Diabetic Retinopathy in Type 2 Diabetic Patients and Likelihood of Developing Diabetic Peripheral Neuropathy

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Abstract

Background: Diabetes mellitus (DM) affects microvasculature, resulting in neuropathy and retinopathy.

Aim: Evaluating the correlation between diabetic retinopathy (DR) and diabetic peripheral neuropathy (DPN) in individuals with type 2 DM (T2DM).

Patients and Methods: An observational cross-sectional study including 60 eyes of T2DM patients aged ≥ 35 years old, categorized according to International clinical diabetic retinopathy severity scale into five groups: [No DR, mild nonproliferative DR (NPDR), moderate NPDR, severe NPDR, and proliferative DR (PDR)]. Modified neuropathy disability score and Baba's diabetic neuropathy classification were used as DPN scoring methods. Thorough clinical ophthalmic and lower limb neurological examinations were done. All patients underwent optical coherence tomography imaging and electrophysiological nerve conduction study. HbA1c, lipid profile, body mass index, and systolic blood pressure were assessed for the participants.

Results: Of the 60 participants with T2DM, DPN occurred 20% more frequently than DR. DPN and DR are significantly interrelated ($P=0.005$), which suggests patients affected by DPN are more susceptible to develop DR. Duration of DM had a significant influence on the prevalence of DR and DPN, with $P<0.001$ and 0.024, respectively. The occurrence of both DR and DPN increased with the increase of HbA1c% and low-density lipoprotein cholesterol concentrations.

Conclusions: DR is more frequently observed in DPN patients than in non-DPN individuals. The severity of DR is strongly correlated to the severity of DPN ($P<0.001$), which suggests that with the increase in DR severity, we can expect a similar increase in DPN severity.

Keywords: Correlation; Diabetic neuropathy; Diabetic retinopathy; Risk factors; Severity

1. Introduction

Diabetes mellitus (DM) is a persistent long term metabolic dysfunction that over time precipitates severe potentially fatal sequelae. Type 2 diabetes mellitus (T2DM), the predominant subtype of diabetes, generally manifests in adulthood due to either insufficient insulin secretion or the development of insulin resistance.¹

The outstanding pathology of DM involves the vasculature, leading to macrovascular pathology such as ischemic heart disease, poor peripheral circulation, and cerebrovascular insults. On the other hand, microvascular complications represented in neuropathy,

retinopathy, and nephropathy are also serious consequences of DM.²

The main ocular complication of DM is diabetic retinopathy (DR), a condition that has a substantial influence on world health.³

After ruling out other potential sources of neuronal damage, patients with DM may exhibit specific signs or symptoms suggestive of neuropathy. This condition is known as diabetic neuropathy.⁴

The most widespread form of peripheral neuropathy is diabetic peripheral neuropathy (DPN), which can cause serious consequences ranging from merely impaired sensation up to limb amputation and, in the worst cases, mortality.⁵

Accepted 15 June 2025.

Available online 31 July 2025

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<https://doi.org/10.21608/aimj.2025.446675>

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As a cytotoxic agent, oxidative stress caused by persistent hyperglycemia activates major pathways incriminated in the etiology of diabetic microvascular complications. These pathways activate reactive oxygen species generation, which in turn causes gene expression alterations, dysregulated autophagy, and the emergence of many molecular drivers of inflammatory cascades that may ultimately result in diabetes-induced microvascular pathologies.⁶

In the current study, we hypothesize that DR and DPN are somehow correlated to one another as they share nearly the same pathogenesis of microvascular insult.

2. Patients and methods

An observational cross-sectional study was conducted at both the Ophthalmology and Rheumatology departments of Al-Zahraa University Hospital, Al-Azhar University, from November 2023 to May 2024. It was conducted in accordance with the World Medical Association Declaration of Helsinki Guidelines and was approved by the Ethics Committee of Al-Azhar University (2023092089). Prior to enrollment, all study candidates underwent a standardized informed consent process, including detailed study information, followed by written consent documentation.

Inclusion criteria: Male and female adults, aged ≥ 35 years old, diagnosed with T2DM.

Exclusion Criteria; Retinopathy and macular edema due to causes other than DM, presence of dense media opacity hindering performing optical coherence tomography (OCT), other types of DM (T1DM, gestational DM, and Pancreatitis-induced DM), chronic arthropathies due to collagen diseases, history of cerebrovascular stroke, systemic illness-associated polyneuropathies (such as thyroid dysfunction and peripheral vascular disease), alcoholism, surgical limb injury, and pregnancy.

All participants were subjected to: History taking/ Assessment of body mass index (BMI) and systolic blood pressure/ Assessment of HbA1c and lipid profile values/ Thorough ophthalmic examination including (refraction, best corrected visual acuity (BCVA), color perception, extra ocular motility, and anterior segment slit lamp examination)/ Fundus examination after achieving maximum pupil dilatation by slit lamp biomicroscope with noncontact 90 D lens and indirect ophthalmoscope/ Colored fundus photography using Topconretinal camera (TRC 50EX, Japan) / Spectral domain OCT imaging (Figure 1) using Optovue OCT (USA, Software version 2016); macular volume and radial scans were acquired to detect morphological features of the macular layers, central foveal thickness (CFT),

and ganglion cell complex (GCC) thickness. Concentric scanning protocol was performed around the optic disc to quantify retinal nerve fiber layer (RNFL) thickness and assess cup-to-disc ratio (CDR) / Clinical neurological examination of both lower limbs (LLs) after asking about symptoms related to DPN [burning/ numbness/ abnormal gait/ frequent falls], inspection of foot ulceration, testing Achilles reflex, and testing sensation [Pin-prick sensation/ vibration perception threshold (VPT)/ temperature sensation] / Nerve conduction study (NCS): using EMG/EP measuring system (Nihon Kohden CO. DC-940BK, 2012, Japan). Motor (common peroneal and tibial nerves) and sensory (sural nerve) conduction studies were bilaterally conducted on both LLs. Velocity, latency, and amplitude of the mentioned nerves were measured (Figure 2).

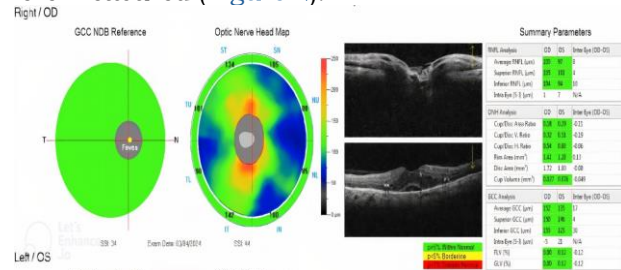


Figure 1. OCT scan of Right eye of a case from the (Proliferative diabetic retinopathy) group, showing macular edema, subfoveal neurosensory detachment and hard exudates, with normal thickness of both retinal nerve fiber layer and ganglion cell complex.

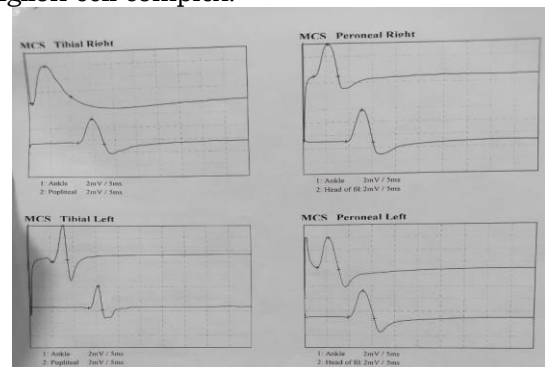


Figure 2. Printout of NCS of a case from the NDR group.

NCS: Nerve conduction study, NDR: No diabetic retinopathy

Regarding DR; the stage of DR was classified based on International Clinical Diabetic Retinopathy (ICDR) and macular edema disease severity scale .. Both eyes of each participant were thoroughly examined and retinopathy grading was given according to the worst eye. The participants were stratified into 5 groups: No DR (NDR), mild nonproliferative DR (NPDR), moderate NPDR, severe NPDR, and PDR.

Regarding the clinical neurological signs, patients were classified according to the Modified

Neuropathy Disability score (mNDS) from grade 0 to grade 10.⁸

Regarding the results of NCS, patients were classified according to Baba's diabetic neuropathy classification (BDC)⁹ from grade 0 to grade 4 (0=No DPN, 1=mild DPN, 2=moderate DPN, 3=moderate to severe DPN, and 4=severe DPN).

Statistical Analysis: Data analysis was carried out utilizing The Statistical Package for The Social Sciences (SPSS) version 29 (IBM Corp., Armonk, NY, USA) for Windows & MedCalc v. 18.

Sample size calculation was based on the expected correlation between DR and DPN in T2DM patients. The required sample size was quantified by applying the following mathematical equation:

$$n = (Z\alpha/2 + Z\beta)^2 / (\text{effect size})^2 + 3$$

Substituting the values into the equation:

$$n = (1.96 + 0.84)^2 / 0.4^2 + 3 = (7.84 / 0.16) + 3 = 52$$

Although the calculated sample size requirement was estimated to be 52 patients, a total of 60 patients were enrolled to account for potential dropouts and ensure adequate power to detect the correlation.

Presentation of quantitative variables adopted the format of average, mean, and standard deviation (SD), while qualitative variables were reported in terms of numbers (NO.) and percentage (%).

Fisher's Exact Test was applied to assess whether there is a significant association between two categorical variables. Spearman's rank correlation was utilized to assess the strength of association and directional relationships between ranked measures. Multivariate Regression Analysis was conducted to model the relationship between the dependent variable (DR or DPN) and multiple independent variables. Statistical significance is attributed to a p-value when it is below 0.05, high significance when <0.001, and no significance when >0.05.

3. Results

The study included 60 eyes of 60 patients of T2DM who were classified according to ICDR severity scale into 5 groups as follows; 11 cases (18.3%) with NDR, 4 cases (6.7%) with mild NPDR, 19 cases (31.7%) with moderate NPDR, 11 cases (18.3%) with severe NPDR, and 15 cases (25%) with PDR. Demographics, clinical profiles, and laboratory parameters of the participants are demonstrated in Table 1.

Among the different DR grades, as the severity of DR increases, BCVA progressively decreases. Poorly dilated pupils with sluggish reaction to light showed a significant correlation with the severity of DR. The correlations between these ocular findings and the severity of DR are shown in Table 2.

On analysis of OCT imaging data, the presence of CME showed a statistically high significant correlation with DR severity ($P < 0.001$). CFT exhibited a moderate positive association with the ICDR severity scale ($\rho = 0.29$, $P = 0.0236$). In contrast, the average RNFL thickness showed a very weak negative correlation ($\rho = -0.07$, $P = 0.6029$), which was not statistically significant. Average GCC thickness had a very weak positive correlation ($\rho = 0.09$, $P = 0.4992$) that was not statistically significant too.

Multiple regression analysis predicting the severity of DR demonstrated that HbA1c% had a significant positive relationship with DR severity and can strongly predict it ($P = 0.001$), while BMI and hypertension (HTN) had statistically nonsignificant correlation with DR severity ($P = 0.842$ and 0.921), respectively.

Out of the 60 participants, 57 cases (95%) had DPN, and only 3 cases (5%) were free from DPN. LL neurological clinical findings and NCS results were summarized in Table 3.

Multiple regression analysis predicting the severity of DPN showed that significant risk factor was HbA1c % ($P = 0.001$), meanwhile, BMI and HTN didn't significantly predict the outcome variable of this study ($P = 0.24$ and 0.373), respectively.

A statistically significant relationship was observed between the presence of DPN and DR ($P = 0.005$), which suggests patients with DPN are more likely to develop DR. (Table 4). The distribution of BDC and the mNDS in the various stages of DR have some clear patterns of existence. The mean BDC increased significantly with the stage of DR severity reflecting the gradient in severity of DPN with advancing severity of DR (Figure 3).

Both the duration of DM and HbA1c level had a highly significant statistical influence on the prevalence of DR and DPN, while age and sex were of no statistical significance correlation with either DR or DPN prevalence as shown in Table 5.

According to Table 6, total cholesterol levels (TCL) and low density lipoprotein cholesterol (LDL) have statistically significant positive correlation with the DR severity. Statistically significant positive associations between BDC and each of TCL, LDL, and triglycerides (TGs) were found.

There is a strong negative correlation between BDC and BCVA (Decimal), indicating that as the severity of DPN increases, visual acuity tends to decrease. Also, color perception showed a statistically significant association with the severity of DPN. Additionally, the correlations between BDC and various OCT parameters were analyzed and all the mentioned results are demonstrated in Table 7.

Table 8 indicates a strong positive correlation between DR severity and each of BDC and mNDS.

A multiple regression analysis was conducted to

investigate whether predicting the DPN severity using the ICDR severity scale, and there was statistically high significant correlation ($P < 0.001$),

which indicates that with the increase of DR severity, we can expect a similar increase in DPN severity (Table 9).

Table 1. Demographic data, medical history, physical data, and laboratory findings of the study groups

VARIABLES		ICDR SEVERITY SCALE					Total
		NDR	Mild NPDR	Moderate NPDR	Severe NPDR	PDR	
PARTICIPANTS: N (%)		11 (18.3)	4 (6.7)	19 (31.7)	11 (18.3)	15 (25)	60
AGE (Y): MEAN (SD)		55.9 (8.6)	63.3 (9.6)	59.7 (6.5)	55.2 (7.6)	59.3 (6.7)	58.3 (7.5)
SEX: N (%)	Male	2 (18.2)	0	6 (31.6)	3 (27.3)	5 (33.3)	16 (26.7)
	Female	9 (81.8)	4 (100)	13 (68.4)	8 (72.7)	10 (66.7)	44 (73.3)
DURATION OF DM (Y): MEAN (SD)		4.5 (4)	14.3 (8.3)	16.4 (7.9)	14.6 (6.1)	16.6 (6.2)	13.8 (7.8)
MEDICATIONS OF DM: N (%)	Insulin	2 (18.2)	1 (25)	6 (31.6)	7 (63.6)	10 (66.7)	26 (43.3)
	OHD	9 (81.8)	2 (50)	9 (47.4)	4 (36.4)	1 (6.7)	25 (41.7)
	Both	0	1 (25)	4 (21.1)	0	4 (26.7)	9 (15)
HYPERTENSION: N (%)		7 (63.6)	3 (75)	9 (47.4)	8 (72.7)	11 (73.3)	38 (63.3)
BMI (KG/M ²): MEAN (SD)		33.4 (6.5)	41 (8.7)	34.6 (7.1)	34.6 (5.7)	34.3 (9.6)	34.7 (7.5)
SBP (MMHG): MEAN (SD)		129.1 (13.4)	138.8 (21.4)	138.4 (16.8)	140 (12.2)	144.7 (12)	138.6 (15)
HBA1C: MEAN (SD)		5.72 (0.53)	7.64 (1.55)	8.27 (0.87)	9 (1.86)	9.7 (1.86)	8.88 (2.01)
TCL (MG/DL): MEAN (SD)		145.4 (41.54)	221.8 (128.65)	202.7 (78.17)	188.3 (70.65)	209.9 (61.3)	192.63 (72.97)
TGS (MG/DL): MEAN (SD)		156.4 (67.54)	211.3 (78.22)	208.4 (228.75)	184.0 (69.93)	188.3 (117.04)	189.57 (146.58)
HDL (MG/DL): MEAN (SD)		44.9 (11.58)	54.5 (24.37)	52.6 (13.53)	52.4 (19.06)	43.5 (12.53)	49.01 (15.06)
LDL (MG/DL): MEAN (SD)		68.5 (35.76)	115.3 (76.77)	113.3 (56.47)	97.2 (57.29)	125.2 (41.65)	105.24 (53.4)

BMI: Body mass index, DM: Diabetes mellitus, HbA1c: Glycosylated Hemoglobin, HDL: High-density lipoprotein cholesterol, ICDR: International Clinical Diabetic Retinopathy, LDL: Low-density lipoprotein cholesterol, N: Number, NDR: No diabetic retinopathy, NPDR: Non-proliferative diabetic retinopathy, OHD: Oral hypoglycaemic drug, PDR: Proliferative diabetic retinopathy, SBP: Systolic blood pressure, SD: Standard deviation, TCL: Total cholesterol level, TGs: Triglycerides

Table 2. Spearman's rank correlation coefficients between the ICDR severity scale and (BCVA/ Pupillary reaction/ Color perception/ Extraocular motility)

VARIABLES	CORRELATION COEFFICIENT	P-VALUE*
BCVA (DECIMAL)	-0.634	<0.001
POORLY DILATED PUPIL WITH SLUGGISH REACTION TO LIGHT	0.324	0.012
RAPD	-0.132	0.315
COLOR PERCEPTION	0.65	<0.001
EXTRAOCULAR MOTILITY	0.174	0.183

* $P > 0.05$: Non-significant, $P < 0.05$: Significant, $P < 0.001$: Highly significant. BCVA: Best corrected visual acuity, ICDR: International Clinical Diabetic Retinopathy, RAPD: Relative afferent pupillary defect

Table 3. Summary of LL neurological clinical findings and NCS

VARIABLE		ICDR SEVERITY SCALE: N (%)					P-value*
		NDR	Mild NPDR	Moderate NPDR	Severe NPDR	PDR	
LOWER LIMB EXAMINATION	Paresthesia	7 (63.6)	2 (50)	15 (78.9)	6 (54.5)	4 (26.7)	0.03
	Abnormal Achilles reflex	2 (18.2)	3 (75)	13 (68.4)	9 (81.8)	15 (100)	<0.001
	Abnormal VPT	7 (63.6)	3 (75)	19 (100)	11 (100)	15 (100)	<0.001
	Abnormal pinprick sensation	4 (36.4)	2 (50)	14 (73.7)	9 (81.8)	15 (100)	<0.01
	Abnormal temperature sensation	4 (36.4)	2 (50)	15 (78.9)	9 (81.8)	15 (100)	0.008
	DFU	0	1 (25)	3 (15.8)	5 (45.5)	8 (53.3)	0.019
NCS	Amputation	0	1 (25)	1 (5.3)	0	4 (26.7)	0.084
	Demyelinating	5 (45.5)	0	3 (15.8)	2 (18.2)	0	0.006
	Axonal	0	0	2 (10.5)	0	0	0.347
	Mixed demyelinating and axonal	3 (27.3)	3 (75)	10 (52.6)	4 (36.4)	4 (26.7)	0.156
	Severe mixed demyelinating and axonal	0	1 (25)	4 (21.1)	5 (45.5)	11 (73.3)	<0.001
	No nerve affection	3 (27.3)	0	0	0	0	
TYPE OF NERVE AFFECTION	Sensory	1 (9.1)	1 (25)	1 (5.3)	0	0	0.009
	Motor	0	1 (25)	0	0	0	
	Sensorimotor	7 (63.6)	2 (50)	18 (94.7)	11 (100)	15 (100)	

*Using Fisher's Exact Test.

$P > 0.05$: Non-significant, $P < 0.05$: Significant, $P < 0.001$: Highly significant.

DFU: Diabetic foot ulcer, ICDR: International Clinical Diabetic Retinopathy, LL: Lower limb, N: Number, NCS: Nerve conduction study, NDR: No diabetic retinopathy, NPDR: Non-proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy, VPT: Vibration perception threshold

Table 4. Prevalence of DPN and DR among diabetic patients

DIABETIC NEUROPATHY	PERIPHERAL	DIABETIC RETINOPATHY: N (%)		TOTAL: N (%)	P-VALUE*
		No	Yes		
NO		3 (27.3%)	0	3 (5)	0.005
YES		8 (72.7%)	49 (100)	57 (95)	
TOTAL		11 (18.3)	49 (81.7)	60 (100)	

*Using Fisher's Exact Test, $P < 0.05$: Significant.

DPN: Diabetic peripheral neuropathy, DR: Diabetic retinopathy, N: Number

Table 5. Association of age, sex, DM duration, and HbA1c with DR and DPN

		DIABETIC RETINOPATHY: N (%)			DIABETIC PERIPHERAL NEUROPATHY: N (%)		
		No	Yes	P-value*	No	Yes	P-value*
AGE (Y)	≥55	6 (54.5)	33 (67.3)	0.4	3 (100)	36 (63.2)	0.306
	<55	5 (45.5)	16 (32.7)	93	0	21 (36.8)	
	Male	2 (18.2)	14 (28.6)	0.7	1 (33.3)	15 (26.3)	1.00
SEX	Female	9 (81.8)	35 (71.4)	1	2 (66.7)	42 (73.7)	
	≥10	1 (9.1)	41 (83.7)	<0.001	0	42 (73.7)	0.024
	<10	10 (90.9)	8 (16.3)		3 (100)	15 (26.3)	
DURATION DM (Y)	≥8	1 (0.09)	40 (81.6)	0.0	0	41 (71.9)	0.001
	<8	10 (0.9)	9 (18.4)	01	3 (100)	16 (28.1)	

*Using Fisher's Exact Test.

$P > 0.05$: Non-significant, $P < 0.05$: Significant, $P < 0.001$: Highly significant.

DM: Diabetes mellitus, DPN: Diabetic peripheral neuropathy, DR: Diabetic retinopathy, HbA1c: Glycosylated Hemoglobin

Table 6. Spearman's rank correlation coefficients between lipid profile and each of ICDR severity scale and BDC

VARIABLES	ICDR SEVERITY SCALE		BDC	
	Correlation Coefficient	P-value*	Correlation Coefficient	P-value*
TCL (MG/DL)	0.283	0.028	0.449	<0.001
TGS (MG/DL)	0.051	0.698	0.357	0.005
HDL (MG/DL)	-0.06	0.649	0.101	0.444
LDL (MG/DL)	0.327	0.011	0.416	0.001

* $P > 0.05$: Non-significant, $P < 0.05$: Significant, $P < 0.001$: Highly significant.

BDC: Baba's diabetic neuropathy classification, DPN: Diabetic peripheral neuropathy, DR: Diabetic retinopathy, HDL: High-density lipoprotein cholesterol, ICDR: International Clinical Diabetic Retinopathy, LDL: Low-density lipoprotein cholesterol, TCL: Total cholesterol level, TGS: Triglycerides

Table 7. Spearman's rank correlation coefficients between BDC and each of ophthalmic examination and OCT variables

VARIABLES	CORRELATION COEFFICIENT	P-VALUE*
BCVA (DECIMAL)	-0.516	<0.001
POORLY DILATED PUPIL WITH SLUGGISH REACTION TO LIGHT	0.270	0.037
RAPD	0.135	0.304
COLOR PERCEPTION	0.468	<0.001
EXTRAOCULAR MOTILITY	0.135	0.304
CFT (μM)	0.112	0.395
RNFL THICKNESS (μM)	-0.155	0.236
AVERAGE GCC THICKNESS (μM)	0.121	0.355

* $P > 0.05$: Non-significant, $P < 0.05$: Significant, $P < 0.001$: Highly significant.

BCVA: Best corrected visual acuity, BDC: Baba's diabetic neuropathy classification, CFT: Central foveal thickness, GCC: Ganglion cell complex, OCT: Optical coherence tomography, RAPD: Relative afferent pupillary defect, RNFL: Retinal nerve fiber layer

Table 8. Spearman's rank correlation coefficients between the ICDR severity scale and each of BDC and mNDS

VARIABLE	SPEARMAN'S RHO	P-VALUE*	SIGNIFICANCE
BDC	0.628	<0.001	Significant at the 0.01 level
mNDS	0.638	<0.001	Significant at the 0.01 level

* $P < 0.001$: Highly significant.

BDC: Baba's diabetic neuropathy classification, ICDR: International clinical diabetic retinopathy, mNDS: Modified neuropathy disability score.

Table 9. Multiple regression analysis predicting the severity of DPN using the ICDR severity scale

PREDICTOR	B	STD. ERROR	BETA	T	P-VALUE*	95% CONFIDENCE INTERVAL
(CONSTANT)	2.847	0.705		4.040	<0.001	1.436 to 4.258
ICDR SEVERITY SCALE	1.794	0.267	0.662	6.728	<0.001	1.260 to 2.328

* $P < 0.001$: Highly significant.

B: Unstandardized beta, DPN: Diabetic peripheral neuropathy, ICDR: International clinical diabetic retinopathy, t: t- test statistic

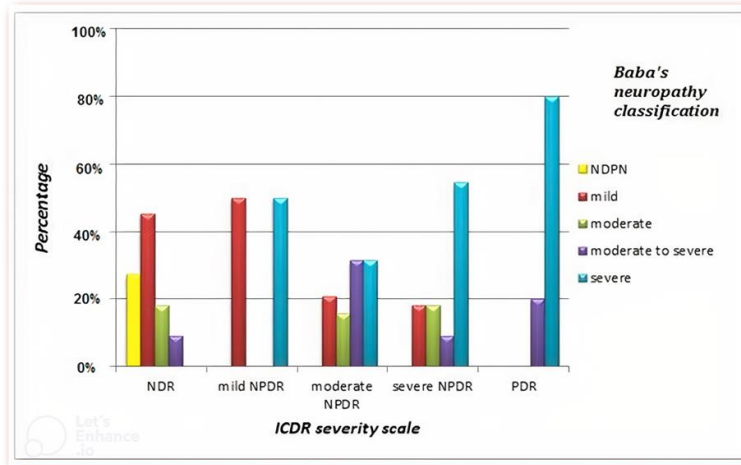


Figure 3. Bar chart illustrating DPN severity (represented by BDC) across all ICDR severity scale levels. ICDR: International Clinical Diabetic Retinopathy, NDPN: No diabetic peripheral neuropathy, NDR: No diabetic retinopathy, NPDR: Non proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy

4. Discussion

DR ranks among the most prevalent microangiopathic complications of DM. It is the major contributor to vision loss in people of working age. The pathogenesis of DR and DPN is almost identical, and the development of any of these complications can determine the severity of the disease.¹⁰

Early detection of DPN symptoms helps prevent neuropathic foot ulcers and the morbidity and mortality from chronic non-healing wounds, which can result in septicemia, local or systemic infection, and even death.⁴

Given that DR and DPN represent the predominant complications of DM, timely detection and management are crucial to mitigate their severe consequences.¹¹

Our results show that 81.7% of the study population had DR, and 95% of them had DPN. DPN occurred 20% more frequently than DR among participants. DR severity showed strong concordance with DPN progression, and we can use the ICDR severity scale to predict the severity of DPN ($P < 0.001$). This conclusion has supported our hypothesis and answered our research question. This strong correlation between these two diabetic complications may be explained by the shared pathophysiological mechanisms and risk factors.

A study conducted by Hafeez et al.¹¹ in 2022 demonstrated that the DR prevalence ratio between DPN-positive and DPN-negative groups was 4.88, indicating a strong statistically significant association between the two morbidities.

Also Iwamoto et al.⁹ have declared in 2022 that

a significant correlation existed between BDC and the occurrence of DR ($P < 0.005$), and BDC grading can be used in predicting DR severity.

Our study revealed that diabetic foot ulcer (DFU) and amputations, which are advanced stages of DPN, were more common in high grades of DR, particularly in PDR, with DFUs in 53.3% of PDR cases ($P = 0.019$).

The current data validate prior observations that Li et al.¹² have found in 2023, while they were exploring the interrelation between DR and DFU development, they found that patients with DR demonstrated higher DFU risk compared to those with no retinopathy (95% CI, 2.33–7.33, $P < 0.001$).

Also, our findings align with previous reports done by Ramsey et al.¹³ in 2022, stating that the development of DFU was strongly linked to DR. Across the studied population, most DFU patients exhibited concurrent DR, with DR patients showing a 2-4 fold higher likelihood of experiencing DFU or other major consequences of diabetic foot pathology. Even more troubling was that DFU and PDR were closely linked to one another, with 31% to 55% of the study cohort experiencing this vision-threatening stage of retinopathy. Besides, NPDR individuals who experienced concomitant refractory DFU were >50% more likely to advance to PDR than those without DFU.

In our study, we underscored the significant influence of DM duration on the prevalence of either DR or DPN as shown in Table 5. In addition, DPN prevalence exceeded DR by a factor of 1.2; based on that, we predict that DPN occurs earlier than DR in our study population. The co-occurrence of DR and DPN exceeded chance

expectation ($P=0.005$), which suggests patients with DPN are more likely to develop DR.

These findings nearly match what Rasheed et al.¹⁴ mentioned 2021, as they observed that DPN occurred 50% more frequently than DR in the study cohort. The study stated that longer DM duration was independently associated with robust odds of DPN occurrence (5.34) compared to DR (3.94), indicating that DPN is more predominant than DR as DM duration gets prolonged. Additionally, there was a significant correlation between the severities of DR and DPN ($P<0.001$).

Our results demonstrated that TCL and LDL had statistically significant correlations with DR severity ($P=0.028$ and 0.011), respectively, while no significant correlations were observed between the ICDR severity scale and TGs or HDL. We also found a statistically significant linear relationship between BDC and each of TCL, LDL, and TGs with p -values <0.001 , 0.001 , and 0.005 , respectively. Conversely, the correlation between BDC and HDL is weak and not statistically significant ($P=0.444$).

As shown by Bourgonje et al.¹⁵ both LDL and HDL levels increased the cumulative incidence of diabetes-associated microangiopathies ($P<0.001$ and 0.002 , respectively). When analyzing each microangiopathic disorder independently, retinopathy was positively linked to LDL levels (95% CI 1.35-8.30, $P=0.009$), while neuropathy was linked with HDL levels (95% CI 1.15-2.70, $P=0.009$).

In our study, age, sex, BMI, and HTN were also analyzed as associated factors for DR and DPN; for DR, there were statistically nonsignificant correlations with the four factors ($P=0.441$, 0.086 , 0.842 , and 0.921), respectively, and similarly for DPN, the correlations with age, sex, BMI, and HTN were of no statistical significance ($P=0.392$, 0.336 , 0.24 , and 0.373), respectively.

A previous study by Patil et al.¹⁶ reported that males and prolonged DM duration were significantly correlated with DR ($P<0.05$), whereas age had no statistically significant correlation with DR ($P>0.05$). Neither age, sex, nor DM duration showed significant associations with DPN incidence.

The current study elucidated that HbA1c% had a significant positive relationship with the ICDR severity scale ($P=0.001$) and highly predicted it. Regarding DPN severity, for every percentage point that HbA1c goes up, the outcome variable goes up by 0.279 units ($P<0.001$).

In parallel to our findings, Almutairi et al.¹⁷ have reported that HbA1c emerged as a significant predictor of DR progression ($P=0.004$).

Also Nozawa et al.¹⁸ demonstrated that DPN progression in T2DM patients showed significant association with the 3-year mean HbA1c levels.

According to our study, OCT imaging revealed that CFT had a moderate positive correlation with the ICDR severity scale ($\rho=0.29$, $P=0.0236$), indicating that increased CFT is associated with increased severity of DR. In contrast, no statistically significant correlations were found between DR severity and each of average RNFL thickness ($\rho=-0.07$, $P=0.6029$) or average GCC thickness ($\rho=0.09$, $P=0.4992$).

In line with our findings, the study conducted by Gupta et al.¹⁹, in which CFT was analyzed amongst diabetics with and without DR, the eyes with DR had considerably higher values than the eyes without DR ($P<0.001$).

Demir et al.²⁰ stated that patients with T2DM had lower RNFL and average GCC thicknesses than controls, although this difference was of no statistical significance ($P>0.05$).

Our study demonstrated a positive correlation ($\rho=0.270$, $P=0.037$) between BDC and poorly dilated pupils with sluggish reaction to light, suggesting that these ocular issues become more prevalent with worsening of DPN.

But our results contradict the claims of Şahin et al.²¹ whose study aimed to investigate the correlation between DPN and pupillary response. In that study, the participants were stratified into three groups: DPN-positive diabetic group, DPN-negative diabetic group, and non-diabetic control group. Pupillometric analysis revealed no significant differences in pupillary diameter across all illumination levels (photopic/ mesopic/ scotopic) among the three groups ($P=0.38$, 0.09 , and 0.05), respectively.

In the current study, the association between BDC and various OCT parameters was evaluated and the results indicated statistically nonsignificant correlation between BDC and each of CFT, average peripapillary RNFL thickness, and average macular GCC thickness ($P=0.395$, 0.236 , and 0.355), respectively.

However, Rasheed et al.¹⁴ have found a statistically significant inverse association between VPT scores (determining DPN severity) and global thickness of ganglion cell inner plexiform layer (GCIPL) ($r=-0.332$, $P<0.02$), superior GCIPL ($r=-0.373$, $P<0.01$), and inferior GCIPL ($r=-0.337$, $P<0.021$), but no statistically significant correlation with average RNFL thickness ($P=0.291$).

Limitations: First, we didn't use OCT angiography, which would give more details about macular and optic disc microvasculature with early detection of ischemic areas and new vessels. Second, we included patients with diabetic macular edema in whom the edema might be a cause of falsely assessing the accurate value of GCC thickness, which gives a hint at early retinal neurodegenerative changes in DR. Third, we didn't assess serum creatinine to

determine the extent to which it is related to the severity of both DR and DPN. Fourth, it is a single-centered study; if we had extended our research beyond our center, we might have discovered a broader range of retinal and neurological signs. Fifth, in this cross-sectional study, we only assessed the HbA1c value once for each T2DM patient, which would not be informative about disease control for a longer duration. Longitudinal study with longer follow up period would have been better in assessing the prognosis of DR and DPN when DM is controlled. Sixth, this study included only 60 patients with T2DM; subsequent studies on a larger scale can be conducted.

Recommendations: Optimizing blood glucose levels, serum lipids, body weight, and blood pressure to mitigate and/or delay the incidence and progression of diabetic microangiopathic sequelae. Applying screening programs for early detection of DR and DPN. A multidisciplinary approach is recommended between Ophthalmologists, Neurologists, and Vascular Surgeons. Patients diagnosed with DR and or DPN should perform further investigations of other complications resulting from DM.

4. Conclusion

The prevalence of DPN is more than DR among the study population; DR is more frequently observed in DPN patients than in non-DPN individuals. The severity of DR is strongly correlated to the severity of DPN ($P < 0.001$), which suggests that with the increase in DR severity, we can expect a similar increase in DPN severity. Both DR and DPN are influenced by HbA1c level, DM duration, and LDL level. Thus, we should keep an eye out for DPN in diabetics presenting to us with DR. Our results advocate for implementing a multidisciplinary approach between Ophthalmologists, Neurologists, and Vascular surgeons to prevent vision loss and disabling limb complications in diabetic patients.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

Funding

No Funds : Yes

Conflicts of interest

There are no conflicts of interest.

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