Original Article

Clinical correlation of diabetic retinopathy with nephropathy and neuropathy

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Purpose: To evaluate the presence of nephropathy and neuropathy in patients with diabetic retinopathy (DR) and to correlate the severity of DR to that of diabetic nephropathy and diabetic neuropathy. **Methods:** This prospective noninterventional hospital-based study included 57 consecutive cases of DR of either sex, presenting to the eye OPD between January 2019 and November 2020 with minimum 5-year duration of Type 1 and 2 DM. Complete ophthalmic examination was done and DR was classified according to early treatment diabetic retinopathy study classification. Severity of diabetic nephropathy was based on urine albumin creatinine ratio and estimated glomerular filtration rate. Severity of diabetic neuropathy was based on nerve conduction velocity. **Results:** The study was conducted on 57 patients of whom patients 45 were males and 12 were females. Mild nonproliferative diabetic retinopathy was present in 22 patients, moderate in 14 patients, severe in 18 patients, and proliferative diabetic retinopathy in 3 patients. In our study, group 30 patients of DR presented without clinically significant macular edema (CSME) and 27 patients presented with CSME. The distribution of severity of DR according to CSME was observed to be statistically significant ($P<<0.05$). The association of severity of DR with severity of diabetic nephropathy was observed to be statistically significant ($P<<0.05$). The association of severity of DR with that of diabetic neuropathy was inconclusive. **Conclusion:** The association of severity of DR with severity of diabetic nephropathy and diabetic neuropathy can be used as a marker for future chronic kidney diseases progression and also to prognosticate neurological outcomes in diabetic patients.

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Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors.[1]

DM is classified on the basis of the pathogenic process leading to hyperglycemia. There are two broad categories of DM, designated as either type 1 or type 2 DM. Type 1 DM develops as a result of autoimmunity against insulin-producing beta cells, resulting in complete or near-total insulin deficiency. Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased hepatic glucose production.[1]

DM can affect multiple organ systems and is responsible for the morbidity and mortality associated with the disease. Diabetes-related complications can be divided into vascular and nonvascular complications and are similar for type 1 and type 2 DM. The vascular complications of DM are further subdivided into microvascular complications like retinopathy, nephropathy and neuropathy, and macro vascular complications like coronary artery disease, peripheral arterial disease, and cerebrovascular disease. Nonvascular complications include infections, skin changes, and hearing loss. Some studies suggest that type 2 DM increases the risk of dementia and impaired cognitive function.

Diabetic retinopathy (DR)

It is estimated that DM affects 7.2–11.4% of the world population, about half of whom have some degree of DR at any given time.[2,3]According to World Health Organization (WHO), DR is responsible for 3–7% of total blindness in Asia.[4] In India, the prevalence of DR in general population is about 3.5%.[5]

There are multiple risk factors that have been associated with the development and progression of DR. Systemic risk factors include duration of diabetes, glycemic control, age, type of DM, hypertension, renal disease, dyslipidemia, pregnancy, anemia, smoking and alcohol. Ocular risk factors include posterior vitreous detachment, cataract surgery, old chorioretinopathy, etc. Duration of DM and degree of glycemic control are the strongest predictors of the development of retinopathy.[6,7] The most commonly used classification for DR is the early treatment diabetic retinopathy study (ETDRS) classification.[8]

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Diabetic nephropathy (DN)

DN is a syndrome comprising of persistent proteinuria, hypertension and a low glomerular filtration rate (GFR).[9] In total, 25–45% of Type 1 DM patients develop nephropathy in their lifespan.[10] The peak time to develop nephropathy is 10–15 years from onset of disease. In patients with type 2 DM, the prevalence of nephropathy is reported to be lower. Nephropathy developed in 50% of type 2 diabetic.[11] This was 20 years after diagnosis and 15% progressed to end stage renal disease. Proteinuria is a known predisposing factor for cardiovascular disease.

Diabetic neuropathy

Peripheral neuropathy is the most common and intractable complication of diabetes.[12] The prevalence of diabetic neuropathy ranges from 7% within 1 year of diagnosis to 50% for those with diabetes for >25 years.[13] If patients with subclinical levels of neuropathic disturbances are included, the prevalence might exceed 90%.

By far the most common diabetic neuropathies are chronic sensorimotor distal symmetric polyneuropathy (DPN) and cardiac autonomic neuropathy. DPN is a length-dependent "dying back" axonopathy, primarily involving the distal portion of the longest myelinated and unmyelinated sensory axons, with relative sparring of motor axons.[14] Therefore, DPN initially affects the distal parts of the lower extremities. With disease progression, sensory loss ascends in the legs and it appears in the hand, causing the typical "stocking and glove" sensory loss.

Purpose

The aim of this study was to evaluate for the presence of nephropathy and neuropathy in patients with DR and to correlate the severity of DR with that of DN and diabetic neuropathy.

Methods

This prospective, hospital based, noninterventional study was conducted in the Department of Ophthalmology, Sardar Patel Medical College and Associated Group of Hospital, Bikaner between January 2019 and November 2020. Permission from institutional review board was taken prior to commencement of study. The study included 57 consecutive cases of DR of either age and sex, presenting to the eye OPD with complaints of diminution of vision. The approval from the ethics committee is obtained and the date of the approval is February 2019.

Inclusion criteria

Patients with minimum 5-year duration of DM giving informed consent for participation in the study were enrolled.

Exclusion criteria

Patients not willing to give informed consent for ophthalmic examination, known cases of DN and diabetic neuropathy, were excluded. Patients suffering from established nephropathy and neuropathy from any other cause including diabetes at the time of presentation were excluded from the study. Media opacities that preclude fundus examination, known case of HTN, urinary tract infection, and patients with a history of ocular inflammation or ocular trauma were excluded.

Sample size

Fifty-seven subjects were recruited in the study. (Note: for nerve conduction velocity (NCV) study, the sample size was 21 as NCV test was not available at our center during COVID 19 pandemic time). Written informed consent was obtained from all the patients.

[A] Ophthalmic evaluation

Standard diagnostic criteria were applied, and investigations like direct and indirect ophthalmoscopy, fundus photography, and OCT were performed after complete clinical examination. Those cases with fundus showing features of DR were graded on the basis of ETDRS classification. Patients with DR were further subclassified into two groups based on presence or absence of clinically significant macular edema (CSME).

[B] For nephropathy:

1. Urine albumin creatinine ratio (U.ACR estimation):- Based on U.ACR value staging of chronic kidney diseases (CKD) was done as normal or mild (<30 mg/24 h), microalbuminuria (30–300 mg/24 h), and macroalbuminuria (>300 mg/24 h).
2. e GFR estimation (calculated by using CKD epidemiology collaboration equation) by using serum creatinine value:- Based on eGFR value, the staging of CKDs were done as Stage-1 CKD (>90 mL/min), Stage-2 CKD (60–89 mL/min), Stage-3A CKD (45–59 mL/min), Stage-3B CKD (30–44 mL/min), Stage-4 CKD (15–29 ml/min), and Stage-5 CKD (<15 mL/min).

[C] For neuropathy:

Nerve conduction study (NCS):- Based on the NCV value of tibial nerve, staging of diabetic neuropathy was done as absent neuropathy (>5 mv), mild neuropathy (2.5–5 mv) and severe neuropathy (<2.5 mv). Treatment was started after confirmation of clinical diagnosis and appropriate referral was done whenever required.

Numerical data was analyzed using the Mann–Whitney test, and categorical variables included Chi-square test. Statistical analyses were performed using primer software (6.0). A *P* value of less than 0.05 was considered to be statistically significant.

Results

Table 1 shows distribution of study population according to severity of DR. Out of 57 patients, 22 patients had mild nonproliferative diabetic retinopathy (NPDR), moderate NPDR in 14 patients, severe NPDR in 18 patients, and proliferative diabetic retinopathy (PDR) in three patients. In this study, out of 57 patients, 33 patients had duration of DM less than 10 years, 17 patients had duration between 11 and 20 years, and

Table 1: Distribution of study population according to the severity of DR

Severity of DR	Frequency	Percentage
Mild NPDR	22	38.60%
Moderate NPDR	14	24.56%
Severe NPDR	18	31.58%
PDR	3	5.26%
TOTAL	57	100%

DR=Diabetic retinopathy, NPDR=Nonproliferative diabetic retinopathy, PDR=Proliferative diabetic retinopathy

Table 2: Distribution of severity of DR according to CSME

Severity of DR	Without CSME	With CSME	Total
Mild NPDR	20	2	22
Moderate NPDR	10	4	14
Sever NPDR	0	18	18
PDR	0	3	3
Total	30	27	57
Chi-square value		38.247	
P-value		0.0001*	

DR=Diabetic retinopathy, NPDR=Nonproliferative diabetic retinopathy, PDR=Proliferative diabetic retinopathy, CSME=Clinically significant macular edema

Table 3: Association of severity of DR with severity/ staging of diabetic nephropathy (eGFR staging)

Nephropathy (EGFR staging)	Mild NPDR	Moderate NPDR	Severe NPDR	PDR
1	8	1	0	0
2	10	4	5	0
3A	2	6	7	0
3B	1	2	4	2
4	0	1	2	1
5	1	0	0	0
Total	22	14	18	3
Chi square value		31.612		
P value		0.007*		

DR=Diabetic retinopathy, NPDR=Nonproliferative diabetic retinopathy, PDR=Proliferative diabetic retinopathy, EGFR=Estimated glomerular filtration rate

Table 4: Association of severity of DR with severity/ staging of nephropathy (UACR staging)

Nephropathy (U ACR staging)	Mild NPDR	Moderate NPDR	Severe NPDR	PDR
Normal (A1)	5	0	0	0
Microalbuminuria (A2)	15	10	6	1
Macroalbuminuria (A3)	2	4	12	2
Total	22	14	18	3
Chi-square value		21.427		
P-value		0.002*		

DR=Diabetic retinopathy, NPDR=Nonproliferative diabetic retinopathy, PDR=Proliferative diabetic retinopathy, U.ACR=Urinary albumin creatinine ratio

Table 5: Association of severity of DR with severity of diabetic neuropathy

Neuropathy	Mild NPDR	Moderate NPDR	Severe NPDR	PDR
Normal	3	2	3	0
Mild	2	1	1	0
Severe	3	1	2	3
Total	8	4	6	3
Chi-square value		5.092		
P-value		0.532		

DR=Diabetic retinopathy, NPDR=Nonproliferative diabetic retinopathy, PDR=Proliferative diabetic retinopathy

7 patients had duration between 21 and 30 years. In patients having bilateral DR, the presentation was asymmetrical and the eye with severe DR was considered.

Table 2 shows distribution of severity of DR according to CSME. Mild NPDR was present in total 22 patients out of which 20 patients presented without CSME and only two patients presented with CSME. Out of total 14 patients of moderate, NPDR only four patients presented with CSME. In case of severe NPDR and PDR, all patients presented with CSME. The distribution of severity of DR according to CSME was observed to be statistically significant ($P<<0.05$).

Table 3 shows association of severity of DR with severity of DN (eGFR staging). In 22 mild NPDR patients, 10 patients had stage 2 CKD. In 14 moderate NPDR patients, six patients had stage 3A CKD. In 18 severe NPDR patients, seven patients had stage 3A CKD. In three PDR patients, two patients had stage 3B CKD. The association of severity of DR with severity/ staging of DN (eGFR staging) was observed to be statistically significant ($P<<0.05$).

Table 4 shows an association of severity of DR with severity of DN (U ACR staging). In mild and moderate NPDR patients, micro albuminuria was present in 15 and 10 patients, respectively. In severe NPDR and PDR, macroalbuminuria was present in 12 and 2 patients, respectively. The association of severity of DR with severity/staging of DN (U ACR staging) was observed to be statistically highly significant ($P<<0.05$).

Table 5 shows an association of severity of DR with severity of diabetic neuropathy. In eight patients without neuropathy, three patients had mild NPDR and three patients had severe NPDR. In four patients of mild neuropathy, two patients had mild NPDR. In nine patients of severe neuropathy, three patients had mild NPDR and three patients had PDR. However, the association of severity of DR with severity of diabetic neuropathy was observed to be statistically nonsignificant ($P > 0.05$).

Discussion

DM is a group of metabolic diseases characterized by hyperglycemia with symptoms of frequent urination, increased thirst, and increased appetite. Depending on etiology of DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system.[1]

The present study was done with primary objective to find the correlation of DR with that of DN and diabetic neuropathy and its association with the severity of retinopathy.

In this study, there was male predominance with 78.95 and 21.05% females. Similar male predominance was also seen in the Chennai urban rural epidemiology study Eye study.[15] The age group of the study population ranged from 31 to 81 years with a mean age of 58.86 year and SD was 9.85.

Among 57 patients, 94.74% had NPDR and 5.26% had PDR. This was comparable to study done by Bhutia *et al*.[16] in Sikkim. In our study population, mild NPDR was present in 22 (38.60%) patients, moderate NPDR in 14 (24.56%) patients, severe NPDR in 18 (31.58%) patients, and PDR in 3 (5.26%) patients.

In our study population, 30 (52.63%) patients of DR presented without CSME and 27 (47.37%) patients presented with CSME. The distribution of severity of DR according to CSME was observed to be statistically highly significant (*P* value 0.0001). Mild NPDR was present in 22 patients out of whom 20 patients presented without CSME and only two patients presented with CSME. Out of 14 patients of moderate NPDR, only four patients presented with CSME. In the case of severe NPDR and PDR, all patients presented with CSME. This significant association indicates that more patients present with CSME in severe grade of DR, while a greater number of patients present without CSME in less severe grade of DR.

In our study, 32 (56.14%) patients present with micro albuminuria followed by 20 (35.09%) patients of macroalbuminuria and 5 (8.77%) patients presented with no albuminuria.

In our study, the association of severity of DR with severity/staging of DN (in both EGFR Staging and U ACR staging) was observed to be statistically highly significant (*P* value 0.007 and 0.002, respectively, in both staging), which indicate that with increasing severity of DR there will be proportional increase in severity of DN also. The mechanism of pathogenesis by which chronic hyperglycemia causes micro vascular complications DR and DN are almost same, so onset and progression of DR and DN are closely related; therefore, in our study, increase in severity of DR is closely related to increase in the severity of DN. Similar findings were observed in a study conducted by Nag *et al*.[17] in which 20.50% patients with diabetes for less than 5 years duration had micro albuminuria and 25.6% had retinopathy. In patients with diabetes for more than 15 years, 90% had micro albuminuria and 100% had retinopathy. Similar association was observed in studies conducted by Lunetta *et al*.[18] and Manaviat *et al*.[19] A number of studies provide evidence that DR may be independently associated with the development of micro albuminuria and, hence, be a powerful predictor for the progression of renal damage in DM patients. El-Asrar *et al*.[20] indicated that the prevalence of DN was found to rise with increasing severity of DR. So, we can conclude that on the basis of severity of DR we can predict the presence/absence and severity of nephropathy in diabetic patients and we can make appropriate referral to nephrologist for subclinical nephropathy in DR patients. Therefore, our study shows that severity of DR increased with the level of albuminuria and is statistically significant. The prevalence of proliferative retinopathy was significantly higher in patients with macroalbuminuria as compared to those with microproteinuria. Singh *et al*.[21] showed that increase in urinary albumin excretion correlates with the development of proliferative retinopathy.

NCSs are the most objective noninvasive measures of nerve function. NCS are strongly correlated with underlying structural changes and are the least subjective and most reliable single criterion standard.[22] NCV is the procedure to measure the speed of electrical impulse conduction through a nerve. This procedure determines whether nerves are normal or nerve damage and destruction are present.[23]

In our study of the 21 patients on whom NCV studies was performed to detect asymptomatic neuropathy, 13 (61.14%) patients were found to have some abnormality, while 8 (38.10%) patients were normal on NCV studies.

In our study, association of severity of neuropathy with severity of DR was observed to be statistically nonsignificant (*P* value 0.532). In eight patients of without neuropathy, three patients had mild NPDR and three patients had severe NPDR. In four patients of mild neuropathy, two patients had mild NPDR. In nine patients of severe neuropathy, three patients had mild NPDR and three patients had PDR. This nonsignificant association could be explained by small sample size for the NCV study (n = 21) as NCV test was not available at our center during COVID 19 pandemic time. Hence, to come to a definite conclusion and establish any relation between DR and neuropathy a large sample size is required.

In our study, out of 13 patients which having diabetic neuropathy 12 patients also had diabetic nephropathy, indicating the probable association and similar pathophysiologic mechanisms for the development of these disorders.

Retinopathy and neuropathy are two most important complications of DM. As both the complications are dealt by two different medical fraternities, a better understanding of the association between the two will help us in its early management and prevention. Although a high prevalence of retinopathy in patients with neuropathy was not found in our study due to small sample size, one must lookout for peripheral neuropathy and it should be kept in mind in diabetics presenting to us with retinopathy.

Conclusion

To conclude, there is a strong correlation between the severity of DR with severity of DN so on the basis of severity of DR we can predict the presence/absence and severity of nephropathy in diabetic patients. Furthermore, in DR patients, even in the absence of proteinuria, we can predict subclinical diabetic nephropathy on the basis of eGFR and we can make appropriate referral to nephrologist for subclinical nephropathy. In our study, no significant association was present between the severity of DR and diabetic neuropathy because of small sample size for NCV study (n = 21) as NCV test was not available at our center during COVID 19 pandemic time. Hence, to come to a definite conclusion and establish any relationship between DR and neuropathy a large sample size is required. However, nephropathy and neuropathy go hand in hand in most of the cases and are associated with retinopathy. A comprehensive care of a patient with DM should include evaluation by ophthalmologist, endocrinologist, nephrologist and neurologist.

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Conflicts of interest

There are no conflicts of interest.

References

1. Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. Harrison's Principles of Internal Medicine. 20th ed. New York (USA): McGraw Hill Education; 2018. Alvin CP, Kevin DN, Carmella EM. Chapter No. 396 Diabetes Mellitus: Diagnosis, Classification, and Pathophysiology; p. 2850.
2. Aiello LP, Gardner TW, King GL, Blankenship G, Cavallerano JD,

Ferris FL 3rd, *et al*. Diabetic retinopathy. Diabetes Care 1998;21:143-56.

3. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of Diabetes. Estimates for the year 2000 and projections for 2030. Diabetes Care 2000;27:1047-53.
4. Meyer JJ, Wang C, Shukla D, Rajendran A, Liang X, Tang S, *et al*. Diabetic retinopathy in Asia. Cataract Refract Surg Today 2005:64-8.
5. Raman R, Rani PK, Rachepalle SR, Gnaanamurthy P, Uthra S, Govindasamy K, *et al*. Prevalence of diabetic retinopathy in India: Sankara Nethralaya diabetic retinopathy epidemiology and molecular genetics study report 2. Ophthalmology 2009;116:311-8.
6. Ryan S. Etiologic mechanisms in diabetic retinopathy. In: Frank RN, editor. Retina. 4th ed. Vol. II. Chapter 66. Philadelphia PA: Elsevier; 2006 p. 1241-65.
7. Al-Bdour MD, Al-Till MI, Abu Samra KM. Risk factors for diabetic retinopathy among Jordanian diabetics. Middle East Afr J Ophthalmol 2008;15:77-80.
8. Olk RJ, Lee CM. Classification of diabetic retinopathy. In: Diabetic Retinopathy: Practical Management. Chapter 2. Philadelphia PA: Lippincott; 1993. p. 5-18.
9. Jawa A, Kcomt J, Fonseca VA. Diabetic nephropathy and retinopathy. Med Clin N Am 2004;88:1001-36.
10. Ismail N, Becker B, Strzelczyk P, Ritz E. Renal disease and hypertension in non–insulin dependent diabetes mellitus. Kidney Int 1999;55:1-28.
11. Orchard TJ, Dorman JS, Maser RE, Becker DJ, Drash AL, Ellis D, *et al*. Prevalence of complications in IDDM by sex and duration. Pittsburgh Epidemiology of Diabetes Complications Study II. Diabetes 1990;39:1116-24.
12. Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, *et al*. Diabetic neuropathies: A statement by the American Diabetes Association. Diabetes Care 2005;28:956-62.
13. Pirart J. Diabetes mellitus and its degenerative complications: A prospective study of 4400 patients observed. Diabetes Care 1978;1:168-88.
14. Sharma RA. Diabetic eye disease in southern India. J Comm Eye Health 1996;9:56-8.
15. Rema M, Srivastava BK, Anitha B, Deepa R, Mohan V. Association of serum lipids with diabetic retinopathy in urban South Indians—the Chennai urban rural epidemiology study (CURES) eye study—2. Diabet Med 2006;23:1029-36.
16. Bhutia KL. Prevalence of diabetic retinopathy in type 2 diabetic patients attending tertiary care hospital in Sikkim. Delhi J Ophthalmol 2017;28:19-21.
17. Nag RN. Association between microalbuminuria and diabetic retinopathy in type 2 diabetic patients; 2011.
18. Lunetta M, Infantone L, Calogero A, Infantone E. Increased urinary albumin excretion is a marker of risk for retinopathy and coronary heart disease in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract 1998;40:45-51.
19. Manaviat MR, Afkhami M, Shoja MR. Retinopathy and microalbuminuria in type II diabetic patients. BMC Ophthalmol 2004;1471-2415.
20. El-Asrar AMA, Rubeaan KAA, Amro SAA, Moharram OA, Kangave D. Retinopathy as a predictor of other diabetic complications. Int Ophthalmol 2002;24:1-11.
21. Singh SK, Bhere A, Singh MK. Diabetic retinopathy and microalbuminuria in lean type 2 diabetes mellitus. J Asso Physicians India 2001;49:439-41.
22. Joshi R. Metabolic syndrome – Emerging clusters of the Indian Phenotype. J Assoc Physicians India 2003;51:445-6.
23. Meijer JW, van Sonderen E, Blaauwwiekel EE, Smit AJ, Groothoff JW, Eisma WH, *et al*. Diabetic neuropathy examination: A hierarchical scoring system to diagnose distal polyneuropathy in diabetes. Diabetes Care 2000;23:750-3.