Section: Medicine

Original Research Article

DIABETIC COMPLICATIONS IN BERHAMPUR, ODISHA: A HOSPITAL STUDY ON RETINOPATHY, NEPHROPATHY, AND NEUROPATHY CORRELATIONS

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Received : 06/08/2023
Received in revised form : 01/09/2023
Accepted : 12/09/2023

Keywords:
Diabetes, Diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, Hospital-based.

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DOI: 10.47009/jamp.2023.5.5.77

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (5); 391-396

Abstract

Background: To assess if nephropathy and neuropathy exist in diabetic retinopathy (DR) patients and to compare the severity of DR with that of diabetic nephropathy and diabetic neuropathy. **Materials and Methods:** This prospective noninterventional hospital-based study comprised 69 patients with DR of either sex who presented to the eye OPD between February 2020 and September 2021 with a minimum 5-year duration of Type 1 and 2 DM. It was conducted in MKCG, Berhampur, Odisha. Following a thorough eye examination, the early treatment diabetic retinopathy research classification of DR was used. Urine albumin creatinine ratio and estimated glomerular filtration rate were used to determine the severity of diabetic nephropathy. Nerve conduction velocity was used to assess the severity of diabetic neuropathy. **Result:** The study involved 69 participants, of whom 54 were men and 15 were women. There were 26 patients with mild nonproliferative diabetic retinopathy, 17 with moderate, 22 with severe, and 4 with proliferative diabetic retinopathy. In our study, 33 patients with CSME and 36 patients with DR presented with clinically significant macular edema. It was found that the distribution of DR severity as determined by CSME, was statistically significant (P 0.05). It was shown that the relationship between DR severity and diabetic nephropathy was statistically significant (P 0.05). There was no conclusive link between the severity of DR and that of diabetic neuropathy. **Conclusion:** The correlation between the severity of DR and the severity of diabetic nephropathy and diabetic neuropathy can be utilized to predict neurological outcomes in diabetic patients as well as the advancement of chronic kidney disease in the future.

INTRODUCTION

A collection of common metabolic illnesses with the phenotype of hyperglycemia are referred to together as diabetes mellitus (DM). A complicated interplay between hereditary and environmental variables leads to several unique forms of diabetes.[1] Based on the pathogenic mechanism that causes hyperglycemia, DM is categorized. DM falls into two basic categories: type 1 DM or type 2 DM. Autoimmune attacks on beta cells that produce insulin cause type 1 diabetes, which is characterized by a complete or nearly complete lack of insulin. Variable levels of insulin resistance, decreased insulin secretion, and increased hepatic glucose production are the hallmarks of the varied group of illnesses known as type 2 diabetes.[1] Multiple organ systems may be affected by DM, which also causes the morbidity and mortality related to the condition. Type 1 and 2 diabetes-related problems can be separated into vascular and nonvascular issues. The vascular problems of DM are further divided into macrovascular complications like coronary artery disease, peripheral arterial disease, and cerebrovascular disease and microvascular complications like retinopathy, nephropathy, and neuropathy. Infections, skin alterations, and hearing loss are examples of nonvascular consequences. According to several research, type 2 diabetes may raise the risk of dementia and cognitive decline.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

One estimate places the prevalence of DM at 7.2-11.4 percent worldwide, with diabetic retinopathy (DR) affecting almost half of the population at any given time.[2,3] The World Health Organization (WHO) estimates that DR causes 3–7% of all blindness in Asia.[4] About 3.5 percent of the overall population in India has DR.[5] The emergence and development of DR have been linked to several risk factors. The length of diabetes, glycemic control, age, type of DM, hypertension, renal illness, dyslipidemia, pregnancy, anemia, smoking, and alcohol are all considered systemic risk factors. Risk factors for the eyes include ancient chorioretinopathy, posterior vitreous detachment, and cataract surgery. The most significant indicators of the onset of retinopathy are the duration of diabetes and the level of glycemic control.[6,7] Early Treatment Diabetic Retinopathy Study (ETDRS) classification is the most popular classification for DR.[8]

The illness known as diabetic nephropathy (DN) includes persistent proteinuria, hypertension, and a low glomerular filtration rate (GFR).[9] Nephropathy affects 25 to 45 percent of Type 1 DM patients throughout their lifetime.[10] Nephropathy is most likely to manifest 10–15 years after the disease first manifests. Nephropathy is said to occur less frequently in persons with type 2 DM. Among type 2 diabetics, nephropathy developed in 50% of cases.[11] 20% had passed since the initial diagnosis, and 15% had advanced to end-stage renal disease. A known risk factor for cardiovascular disease is proteinuria. The most prevalent and untreatable consequence of diabetes is peripheral neuropathy.[12] Diabetic neuropathy affects 7 percent of people within a year of diagnosis and 50 percent of those with diabetes who have had the disease for more than 25 years.[13] The prevalence could surpass 90% if patients with subclinical neuropathic abnormalities are included. Chronic sensorimotor distal symmetric polyneuropathy (DPN) and cardiac autonomic neuropathy are the two most prevalent diabetic neuropathies. With relative sparing of the motor axons, DPN is a length-dependent "dying back" axonopathy that primarily affects the distal portion of the longest myelinated and unmyelinated sensory axons.[14] DPN thus initially impacts the lower extremities' distal regions. As the disease progresses, sensory loss in the hands and legs goes, leading to the classic "stocking and glove" sensory loss.

Objective

This study aimed to determine whether individuals with DR had nephropathy and neuropathy and compare the severity of DR to that of DN and diabetic neuropathy.

MATERIALS AND METHODS

This prospective, hospital-based study was conducted in the Maharaja Krishna Chandra Gajapati Medical College & Hospital, Berhampur, between February 2020 and September 2021. Before the start of the trial, institutional review board approval was obtained. The study comprised 57 cases of DR that presented to the eye OPD in a row with symptoms of vision loss, regardless of age or sex. The ethics committee's clearance was received and was given in February 2019.

Inclusion Criteria

Patients who provided informed consent to participate in the trial and had DM for at least five years were included.

Exclusion Criteria

Patients unwilling to consent to an ocular examination, those with known DN, and those with diabetic neuropathy were eliminated. Patients with diabetes at the time of presentation and those with preexisting nephropathy and neuropathy from any other cause were excluded from the research. Patients with known cases of HTN, urinary tract infections, media opacities that prevent fundus inspection, and patients with a history of ocular inflammation or trauma were excluded.

Sample Size

In total, 69 participants were chosen for the study. (Note: for the nerve conduction velocity (NCV) study, the sample size was 25 as the NCV test was unavailable at our centre during the COVID-19 pandemic). From each patient, written informed consent was gained.

Ophthalmic Evaluation

Following a thorough clinical examination, standard diagnostic criteria were used, and procedures such as direct and indirect ophthalmoscopy, fundus photography, and OCT were carried out. The ETDRS categorization was used to assign grades to those cases when the fundus had characteristics of DR. DR patients were subsequently divided into two groups according to whether or not they had clinically significant macular edema (CSME).

For Nephropathy

Urinary albumin to creatinine ratio (U.ACR estimate): Chronic kidney disease (CKD) staging was done as usual or moderate (30 mg/24 h), microalbuminuria (30-300 mg/24 h), and macroalbuminuria (>300 mg/24 h) based on U.ACR values.

e GFR estimate utilizing the serum creatinine value and the CKD epidemiology collaboration equation

- CKDs were staged 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) based on eGFR values.

For Neuropathy

NCS (nerve conduction study): Diabetic neuropathy was staged as absent neuropathy (>5 mv), mild neuropathy (2.5-5 mv), and severe neuropathy (2.5 mv) based on the NCV value of the tibial nerve. Following the validation of the clinical diagnosis, the necessary referral was made if needed.

The Mann-Whitney test was used to evaluate numerical data, and the Chi-square test was used to analyze categorical data. Statistical evaluations were

ISSN (O): 2687-5365; ISSN (P): 2753-6556

carried out utilizing the primer software (6.0). Statistical significance was defined as a P value less than 0.05.

RESULTS

The distribution of the research population by DR severity is shown in Table 1. Twenty-six of the 69 patients had mild nonproliferative diabetic retinopathy (NPDR), seventeen had moderate NPDR, 22 had severe NPDR, and four had proliferative diabetic retinopathy (PDR). Out of 69 patients in this study, 40 had diabetes for less than ten years, 21 had it for between 11 and 20 years, and 8 had it for between 21 and 30 years. The presentation was asymmetrical in individuals with bilateral DR, and the eye with the most severe DR was considered [Table 1].

The distribution of DR severity according to CSME is seen in Table 2. There were 27 patients with mild NPDR in total. However, only two individuals had CSME, and 25 patients had mild NPDR but did not have CSME. Only five of the 16 moderate patients who had NPDR had CSME. All patients who had significant NPDR and PDR presented with CSME. It was found that the distribution of DR severity, as determined by CSME, was statistically significant (P 0.05) [Table 2].

The severity of DR is correlated with the severity of DN in Table 3. (eGFR staging). 12 of the 27 individuals with mild NPDR had stage 2 CKD. Seven of the 17 individuals with moderate NPDR had stage 3A CKD. Eight of the 22 patients with severe NPDR had stage 3A CKD. Two of the three PDR patients had stage 3B CKD. It was shown that there was a statistically significant (P 0.05) correlation between the severity of DR and the severity/stage of DN (eGFR staging) [Table 3].

Table 4 displays a correlation between the severity of DR and the severity of DN (U ACR staging). Microalbuminuria was seen in 18 and 12 patients with mild and moderate NPDR, respectively. Macroalbuminuria was seen in 14 and 2 individuals, respectively, with severe NPDR and PDR. It was shown that the relationship between the severity of DR and the severity/stage of DN (U ACR staging) was statistically highly significant (P 0.05) [Table 4].

A correlation between the severity of diabetic neuropathy and the severity of DR is seen in Table 5. Four individuals had mild NPDR, and four had severe NPDR among 11 patients without neuropathy. Two of four individuals with mild neuropathy had mild NPDR. Four individuals had mild NPDR, and four patients had PDR in the eleven patients with severe neuropathy. However, it was found that there was no statistically significant relationship between the severity of DR and the severity of diabetic neuropathy (P > 0.05) [Table 5]

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

	Severity of DR	Frequency	Percentage
1.	Mild NPDR	26	37.68116
2.	Moderate NPDR	17	24.63768
3.	Severe NPDR	22	31.88406
4.	PDR	4	5.797101
	Total	69	100

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

Table 2: Distribution of severity of DR according to CSME

	Severity of DR	Without CSME	With CSME	Total	Chi-square value, P-value
1.	Mild NPDR	25	2	27	37.911, 0.0001*
2.	Moderate NPDR	11	5	16	
3.	Severe NPDR	0	22	22	
4.	PDR	0	4	4	
	Total	36	33	69	

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

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	Total	Chi-square value, P-value
1.	1	10	1	0	0	11	31.701, 0.007*
2.	2	12	5	6	0	23	
3.	3A	1	7	8	0	18	
4.	3B	1	3	5	2	11	
5.	4	0	1	3	1	5	
6.	5	1	0	0	0	1	
	Total	27	17	22	3	69	

ISSN (O): 2687-5365; ISSN (P): 2753-6556

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

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	Total	Chi-square value, P-value
1	Normal (A1)	6	0	0	0	6	20.317, 0.002
2	Microalbuminuria (A2)	18	12	8	1	39	
3	Macroalbuminuria (A3)	3	5	14	2	24	
	Total	27	17	22	3	69	

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	Chi-square value, P-value
1	Normal	4	3	4	0	5.089, 0.521
2	Mild	2	1	1	0	
3	Severe	4	1	2	4	
	Total	10	5	7	4	

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

DISCUSSION

A category of metabolic illnesses known as DM is hyperglycemia-related and manifests as increased thirst, hunger, and urine frequency. Depending on the etiology of DM, impaired insulin secretion, decreased glucose utilization, and increased glucose generation are all variables that contribute to hyperglycemia. The secondary pathophysiologic alterations in numerous organ systems brought on by the metabolic dysregulation associated with DM place a heavy strain on the diabetic and the healthcare system.[1]

The main goal of the current investigation was to determine the relationship between diabetic retinopathy and the severity of DN and diabetic neuropathy. Males comprised 77.85 percent of the study's participants, compared to 22.15 percent of females. The Chennai urban, rural epidemiological research Eye study also revealed a similar male prevalence.[15] The research population's age ranged from 30 to 79 years, with a mean age of 57.96 years and a standard deviation of 9.78 years. 95.20 percent of the 69 patients had NPDR, while 5.79 percent had PDR. Comparable research was done by Bhutia et al. in Sikkim.[16] Twenty-six individuals in our study population had mild NPDR (37.68 percent). Patients were found to have PDR in 4 (5.79%), moderate NPDR in 17 (24.63%), severe NPDR in 22 (31.88%), and severe NPDR in 22 (31.88%) patients.

In our study population, 33 (47.82 percent) and 36 (52.17 percent) patients with DR, respectively presented with and without CSME. It was found that the CSME distribution of DR severity was statistically very significant (P value 0.0001). Only two out of the 27 patients with mild NPDR had CSME, while the other 25 had mild NPDR. Only five patients with CSME were present out of 16 with moderate NPDR. All patients who had significant NPDR and PDR presented with CSME. This statistically substantial connection suggests that whereas more individuals come without CSME in less severe grades of DR, more patients present with CSME in uphill grades of DR.

In our study, there were 39 (56.52%) patients with microalbuminuria, 24 (34.78%) patients with macroalbuminuria, and 6 (8.69%) patients with no albuminuria.

In our study, the relationship between DR severity and DN severity/staging (in both EGFR staging and U ACR staging) was statistically highly significant (P values 0.007 and 0.002, respectively, in both stage). This finding suggests that DN severity will also increase proportionately as DR severity increases. The pathophysiology of microvascular problems brought on by persistent hyperglycemia Since DR and DN are almost identical, their onset and progression are very tightly associated. Accordingly, in our study, an increase in DR severity strongly correlates with an increase in DN severity. Similar results were found in research by Nag et al., which found that 25.6% of individuals with diabetes for less than five years had retinopathy and 20.50% had microalbuminuria.[17] In patients with diabetes for over 15 years, 90% had microalbuminuria, and 100% had retinopathy. Similar associations were found in investigations by Manaviat et al. and Lunetta et al,[18,19] Numerous studies show that DR may independently be linked to the emergence of microalbuminuria and, as a result, be a potent indicator of the development of renal impairment in DM patients. According to El-Asrar et al., the prevalence of DN was found to increase as DR severity increased.[20] Therefore, We can conclude that we can forecast the presence and severity of nephropathy in diabetic patients based on the severity

ISSN (O): 2687-5365; ISSN (P): 2753-6556

of their DR, and we can appropriately send individuals with subclinical nephropathy to nephrologists. As a result, our study found that the degree of albuminuria enhanced the severity of DR, which is statistically significant. Individuals with macroalbuminuria had a considerably higher prevalence of proliferative retinopathy than patients with microproteinuria. According to research by Singh et al., the progression of proliferative retinopathy is correlated with an increase in urine albumin excretion.[21]

The most impartial noninvasive assessments of nerve function are NCSs. The least subjective and most accurate single criterion standard is the NCS, which has a high correlation with underlying structural alterations.[22] The NCV technique measures how quickly an electrical impulse travels through a nerve. This treatment reveals whether nerves are healthy or whether there is nerve deterioration and injury.[23]

15 (60.0 percent) of the 25 patients in our study who had NCV studies done to look for asymptomatic neuropathy had some abnormalities, while 10 (40.0 percent) had regular NCV studies.

In our investigation, we found no statistically significant relationship between the degree of neuropathy and the severity of the DR (P value 0.532). Four patients had mild NPDR, and four had severe NPDR in the eleven patients without neuropathy. Two of four individuals with mild neuropathy had mild NPDR. Four individuals had mild NPDR, and four patients had PDR in the eleven patients with severe neuropathy. The NCV study's limited sample size (n = 21), which can be attributed to the NCV test not being available at our center during the COVID-19 pandemic, may help to explain this nonsignificant connection. Therefore, a large sample size is needed to draw firm conclusions and prove any association between DR and neuropathy.

13 of the 15 patients in our study who had diabetic nephropathy also had diabetic neuropathy, showing a likely link and similar pathophysiologic pathways for the onset of these illnesses.

The two most significant side effects of DM are retinal disease and neuropathy. A more profound comprehension of the relationship between the two will aid in their early care and prevention because two separate medical fraternities handle both issues. Although our study's small sample size prevented us from detecting a significant prevalence of retinopathy in patients with neuropathy, peripheral neuropathy should be suspected in people with diabetes who present to us with retinopathy.

CONCLUSION

As a result, we can predict the presence/absence and severity of nephropathy in diabetic patients based on the severity of the DR. There is a substantial association between the severity of DR and the severity of DN. Additionally, we can use eGFR in DR patients to predict subclinical diabetic nephropathy and appropriately refer patients to nephrologists for subclinical nephropathy, even in the absence of proteinuria. As the NCV test was not available at our site during the COVID-19 pandemic, there was no statistically significant correlation between the severity of DR and diabetic neuropathy in our study (n = 25). Therefore, a large sample size is needed to draw a firm conclusion and demonstrate any association between DR and neuropathy. However, nephropathy and neuropathy frequently coexist and are connected to retinopathy. A patient with DM needs to receive comprehensive care, which includes evaluations by ophthalmologists, endocrinologists, nephrologists, and neurologists.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556