ORIGINAL RESEARCH ARTICLE

Prevalence and Association of Diabetic Retinopathy and Diabetic Peripheral Neuropathy in Indian Type 2 Diabetes Mellitus Subjects Attending Tertiary Diabetic Institute

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A B S T R A C T

Introduction: Several studies have reported that diabetic peripheral neuropathy is more common than other diabetic microvascular complications. Finding an association between diabetic peripheral neuropathy (DPN) and diabetic retinopathy (DR) may help in early diagnosis of each of these devastating microvascular complications and estimate their severity. With the lack of literature on these aspects we conducted a study to estimate the occurrence of DR and DPN, to find their association and to identify their risk factors in people with type 2 diabetes mellitus (T2DM).

Material and Methods: A retrospective observational study was conducted for all the diagnosed cases of type 2 diabetes subjects aged above 30 years at Karnataka Institute of Endocrinology and Research (KIER), Bengaluru, India. The details on clinical and laboratory investigations of 400 patients were studied and the data was collected.

Results: 54.0% had DR and 50.8% had DPN. The proportion of cases with DPN (61.6%) among the patients having DR was significantly higher compared to those with no neuropathy (46.2%). The odds ratio revealed two times significant higher probability of coexisting DPN among those with DR. DR was significantly associated with males and long duration of DM.

Conclusion: We conclude a close association of diabetic retinopathy and diabetic peripheral neuropathy. Hence we suggest screening of DR in patients with DPN and vice versa.

Keywords: Diabetic Retinopathy (DR), Diabetic Peripheralneuropathy (DPN), Diabetesmellitus (DM), Type 2 Diabetes Mellitus (T2DM), Karnataka Institute of Endocrinology and Research (KIER).

INTRODUCTION

Diabetes and related complications are associated with long term damage and failure of various organ systems. The pathological hallmark of diabetes mellitus involves the vasculature leading to both micro-vascular and macro-vascular complications.[1] Chronicity of hyperglycemia is associated with long-term organ damage and failure; mainly eyes, nerves, kidneys and the heart.[2] Diabetic retinopathy and diabetic peripheral neuropathy are the two most commonly encountered microvascular complications of diabetes mellitus.[3] DR is a major cause of preventable blindness in both developing and developed countries. Diabetic neuropathy involves both peripheral and autonomic neurons, affecting almost half of population[4] with diabetes. Considering a common patho-physiological substratum among the microvascular chronic complications of diabetes (neuropathy, retinopathy)[5,6], we expect certain degree of inter-correlations between their occurrence, onset or the severity of one over the other. Above all, they are diagnosed and managed by physicians of different specialties. The physicians might sometime fail to address complications related to other specialty and hence patients might remain non-referred[7]. Hence, this study was conducted to find the occurrence and association between DR and DPN. The outcome of this study is expected to be an informed recommendation for inter-specialty management of complications that have a common patho-physiological substratum.

Study objectives were to estimate the prevalence of diabetic retinopathy and diabetic peripheral neuropathy and to study the association between them.

MATERIAL AND METHODS

A retrospective observational study was conducted among all the diagnosed cases of T2DM subjets 30 years and above at KIER, Bengaluru during the study period between May, 2018 and January, 2019 at KIER, Bangaluru.

Considering the prevalence of DN as 39% as per the previous

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study conducted at a tertiary care center Bangalore[8], with 95% confidence interval and permissible error - absolute precision of 6% (L), sample size of 254 was calculated using the formula $n=z^2(pq/L^2)$, where, z=1.96 at 95% confidence interval, p = estimated prevalence (39%), q=100-p and L = (6% absolute precision). The total sample size of 253.76 ≈ 254 was considered for the study.

Inclusion criteria

1. All the diagnosed cases of T2DM screened for DR and DPN at KIER,
2. Age 30 years and above.

Exclusion criteria

1. Chronic alcoholics.
2. Tobacco users.
3. HIV positive patients and patients on HAART.
4. Pregnant women.

The patients were screened for retinopathy by fundus examination by the ophthalmologist and were graded as DR, NPDR, CSME. Those screened for DPN by 10g monofilament test and biothesiometer were graded as mild, moderate and severe. The data was collected from electronic medical records.

Operational Definitions:

a. Type 2 Diabetes

i. FBS- Fasting blood glucose: ≥126 mg/dL(7.0 mmol/L). (Fasting defined as no caloric intake for at least 8 hours).
ii. PPBS- Two-hour postprandial glucose: ≥200 mg/dL(11.1mmol/L).
iii. HbA1c: > 6.5%.

b. Diabetic Retinopathy

Definition and Grades:[9,10,11]Standard techniques and equipment were used for clinical examination; retinal evaluation was done using an indirect ophthalmoscope or 90D lens on slit lamp or by fundus photography. Grading of the retinopathy was done using International Clinical Diabetic Retinopathy Disease Severity Scale Classification.

No apparent Retinopathy: No abnormalities

Non-proliferative diabetic retinopathy (NPDR): The presence of hemorrhages, micro-aneurysms, hard exudates, soft exudates, venous bleeding and intra-retinal microvascular abnormality.

Mild NPDR: Microaneurysms only.

Moderate NPDR: More than just microaneurysm but less than severe NPDR.

Severe NPDR: Any of the following, a) more than 20 intra-retinal hemorrhages in each of 4 quadrants, b) definite venous beading in 2+ quadrants, c) prominent IRMA in 1+ quadrants.

Proliferative diabetic retinopathy (PDR): One or more of the following:

1. Neovascularization,
2. Vitreous/ pre-retinal hemorrhage.

c. Diabetic Peripheral Neuropathy - Definition and Grades: Neuropathy was assessed using 10g monofilament, pinprick sensations, ankle reflexes, temperature and vibration perception threshold (VPT) test. The 10g Vonfrey monofilament was placed perpendicular to the skin and pressure was applied until the filament just buckled with a contact time of 2 seconds. Inability to perceive the sensation at any one site was considered abnormal. In addition, ankle reflexes were also assessed with a percussion hammer and recorded as either present or absent.

Initially, each person with T2DM was confirmed by the physician to have DPN if diagnosed with one or more abnormal finding of 10g monofilament, pinprick sensations temperature perception and ankle reflexes. Thereafter, the patient underwent VPT test to categorize them according to the severity level of DPN.

Quantification of DPN was assessed by VPT using a Biothesiometer a standardized manner by a single observer for all the participants. VPT was then measured at five different locations on the feet of both legs. If the great toe was affected by ulcer, VPT was measured at the base of the first, third or fifth metatarsals. The voltage was slowly increased at the rate of 1 mV/s, and the VPT value was defined as the voltage level when the participant indicated that he or she first felt the vibration sense. The mean value of five measurements of both legs were calculated and considered for analysis considering the patient's age, and accordingly the patients were categorized into the grades of DPN. In the participants with DPN diagnosis established earlier, the year of neuropathy diagnosis was taken from the patients' previous records.

A cutoff value of 20 mV was considered for the presence of DPN. Then graded as mild, moderate and severe based on VPT score. The cutoff value of 20 mV of VPT in the Indian population was found to have better sensitivity compared to Neuropathy Disability Scores (NDS) taken as the gold standard.[12]

STATISTICAL ANALYSIS

All the data collected was entered into an Excel spreadsheet. The continuous data like age, duration of diabetes, HbA1c levels were expressed in the form of mean and standard deviation. The discrete data like proportion of patients with DR, DPN, males and females and other risk factors were expressed in percentages. Univariate association of the continuous variables with retinopathy and neuropathy were assessed using independent t-test and Chi-square test for categorical variables. Logistic regression was applied to find the risk of association in terms of Odds Ratio (OR). The analysis was conducted using SPSS version 16.0. A p-value of <0.05 was taken as statistically significant.

RESULTS

The mean age of study participants was nearly 56 yrs and it ranged from a minimum of 35 yrs to a maximum of 80 yrs. Majority of them were in the age group of 55-64 yrs (36.5%) and were males (65.0%). The mean duration of DM was nearly 10 yrs and it ranged from newly detected cases to a maximum of 38 yrs of diabetes. (Table-1)

More than half of the (54.0%) people with diabetes had diabetic retinopathy. Among them major proportions had both the ends of the spectrum of severity of diabetic retinopathy i.e., the lower end of the severity being mild NPDR (32.8%) and the other end of the severity being PDR (32.0%), followed by equal proportions of moderate (18.0%) and severe NPDR (17.2%) were noted. (Tables 2 & 3)

Particulars	n (%)
Mean age in years¥	55.88±10.04
Age group	
35 - 44 yrs	66 (16.5)
45 - 54 yrs	102 (25.5)
55 - 64 yrs	146 (36.5)
65 – 74 yrs	74 (18.5)
≥75 yrs	12 (3.0)
Gender (%)	
Males	260 (65.0)
Females	140 (35.0)
Mean duration of DM¥	9.79±7.29
¥ - Mean	

Table-1: Distribution of the study participants based on age, gender and duration of diabetes

Similar to DR, more than half of the patients with diabetes also had DPN (50.8%) among whom majority had severe grade of peripheral neuropathy (37.4%) followed by mild (35.5%) and moderate grade (27.1%). (Tables 2 & 3)

In the present study, 57.8% of those with diabetic retinopathy had diabetic peripheral neuropathy and 60.1% of those with diabetic neuropathy had diabetic retinopathy. Among the patients having diabetic retinopathy, the proportions of patients with neuropathy (61.6%) was significantly higher compared to those with no neuropathy (46.2%). The odds ratio revealed that, the patients with diabetic retinopathy had nearly 2 times significant higher probability of coexisting neuropathy (P<0.05). (Table 2)

Among 400 patients with T2DM, both DR and DPN was present among 125 i.e., 31.2% of them, DR alone was present in 91 i.e., 22.7% and DPN in 106 i.e., 26.5% patients. (Table 2)

DR was significantly associated with males and longer duration of DM (P<0.05). Though age was not significantly associated with DR, majority (57.5%) belonged to older age group i.e., more than 55 years (P>0.05). (Table 4A) The age of those with DR (≈ 57 yrs) was not significantly different compared to those without DR (≈ 55 yrs) (P>0.05) but, the duration of diabetes was significantly higher among those

Diabetic Retinopathy	Diabetic Peripheral Neuropathy		Total	Odds Ratio (P-value)
	Yes	No		
Yes	125 (61.6%)	91 (46.2%)	216 (54.0%)	1.94 (0.002)*
No	78 (38.4%)	106 (53.8%)	184 (46.0%)	
Total	203 (50.8%)	197 (49.2%)	400 (100.0%)	
*indicates significant association at P<0.05				

Table-2: Estimated prevalence and association of co-existence of diabetic retinopathy and peripheral neuropathy among the type 2 diabetes patients

Complications	Grades of Severity			
	Mild	Moderate	Severe	PDR
Diabetic Retinopathy¥ (n=216)	71 (32.8)	39 (18.0)	37 (17.2)	69 (32.0)
Diabetic Neuropathy (n=203)	72 (35.5)	55 (27.1)	76 (37.4)	-
¥ - Mild indicates mild NPDR (V); Moderate indicates moderate NPDR; severe indicates severe NPDR; PDR (proliferative diabetic retinopathy) indicates the highest grade of severity				

Table-3: Different grades of severity of diabetic retinopathy and peripheral neuropathy among the type 2 diabetes patients

Table 4A

Complications	Diabetic Retinopathy		χ^2 – value (P- value)
	Present	Absent	
Age in years			
≤ 55	89 (49.7)	90 (50.3)	2.39 (0.07)
> 55	127 (57.5)	94 (42.5)	
Gender			
Males	159 (61.2)	101 (38.8)	15.31 (<0.0001)*
Females	57 (40.7)	83 (59.3)	
Duration of diabetes in years			
< 10	84 (38.5)	134 (61.5)	46.15 (<0.0001)*
≥ 10	132 (72.5)	50 (27.5)	
*indicates significant statistical association at P<0.05			

Table 4B

Complications	Diabetic Neuropathy		χ^2 – value (P- value)
	Present	Absent	
Age in years			
≤ 55	93 (52.0)	86 (48.0)	0.19 (0.67)
> 55	110 (49.8)	111 (50.2)	
Gender			
Males	141 (54.2)	119 (45.8)	3.60 (0.06)
Females	62 (44.3)	78 (55.7)	
Duration of diabetes in years			
< 10	108 (49.5)	110 (50.5)	0.28 (0.62)
≥ 10	95 (52.2)	87 (47.8)	

Table-4: Association of age, gender and duration of diabetes with the presence of retinopathy (4A) and neuropathy (4B)

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	Severity of Diabetic Retinopathy	Severity of Diabetic Neuropathy
Duration of diabetes	0.36 (<0.0001)*	0.05 (0.33)
* indicates significant statistical correlation at P<0.05		

Table-5: Correlation of duration of diabetes with the severity of retinopathy and neuropathy

with DR (≈ 12 yrs) compared to those with no DR (≈ 7 yrs) (*P*<0.05).

In case of DPN, significant association was not seen with age, gender and duration of diabetes. However majority belonged to lower age group (52.0%) and were males (54.2%). Similarly, major proportion also had longer duration of disease (52.2%). (Table 4B) The age and duration of diabetes of those with and with no DPN were same i.e., 56 yrs and 10 yrs respectively (*P*>0.05).

The severity of DR increased significantly with the duration of diabetes (*P*<0.05), however the severity of DPN also increased but was not significant (*P*>0.05). (Table 5)

DISCUSSION

Diabetic retinopathy and diabetic peripheral neuropathy both having the same pathogenesis, the occurrence of any one complication could reflect either the presence or may even reflect the severity of other complication in an individual. Understanding such association between both complications helps us in their prevention and early management, as their early detection and effective treatment may reverse the event to a certain extent.[7] Thus to elicit the extent of coexistence of diabetic retinopathy and diabetic peripheral neuropathy and also to elicit the association between the two, the current study was taken up.

The mean age of participants in this study was nearly 56 yrs with a range of 35 - 80 yrs and majority were males (65.0%). In a previous two studies exploring the association between neuropathy and retinopathy in diabetes, Abdollahi A et al., reported the mean age of the patients as 58 yrs and a range of 40-78 years was observed[13]and Sharma VK et al., noted majority as males (58% ≈ 60%).[7]

The mean duration of DM was nearly 10 yrs in this study and it ranged from newly detected cases to a maximum of 38 yrs of diabetes and is in line with the findings by Abdollahi A et al. wherein the duration of diabetes was 12.8 years (range 1 to 35).[13]

More than half of our (54.0%) diabetic patients had diabetic retinopathy. Among them major proportions had both the ends of the spectrum of severity of diabetic retinopathy i.e., the lower end of the severity being mild NPDR (32.8%) and the other end of the severity being PDR (32.0%), followed by equal proportions of moderate (18.0%) and severe NPDR (17.2%) were noted. Qureshi T et al., noted prevalence of any DR among known diabetics as 27%.[14] A hospital-based, cross-sectional study showed that the prevalence of diabetic retinopathy (DR) was 31.5% wherein, NPDR was seen among 22.5% and PDR among 9.0%, in type 2 DM patients.[15] However a higher prevalence as compared to population based epidemiological studies was noted (18.0%) which may be due to the probable existence of referral bias among the diabetic patients who were reported to tertiary care centers i.e., with larger number of people with diabetics reporting to the tertiary hospital, chances of prevalence of complications may also be larger.[15,16,17]

More than half (50.8%) of the patients in the current study had peripheral neuropathy however Bansal D et al., reported diabetic peripheral neuropathy in 29.2% of them. Majority had moderate grade followed by mild and severe however in our study majority had severe grade followed by mild and moderate. The difference in the prevalence may be due to different durations of diabetes.[12]

In this study, 57.8% of those with DR had DPN and 60.1% of those with DPN had DR. Gokhale VS et al.,[9] noted DR among 76% of those with proven diabetic neuropathy and Abdollahi A et al.,[13] reported that 78.1% of patients with retinopathy had DPN and 79.1% of patients with DPN had retinopathy. The proportions in earlier studies were slightly higher compared to our study which may be due to difference in the duration of diabetes and age of the study participants. Among the patients having DR, this study found the proportions of diabetics with peripheral neuropathy (61.6%) were significantly higher compared to those with no neuropathy (46.2%) and the patients with diabetic retinopathy had nearly 2 times significant higher probability of coexisting neuropathy. Similarly, Sharma VK et al., found prevalence of DR 2.75 times more in cases with DPN (37%) compared to those without DPN (14%). They also noted that 21.0% had both DR and DPN, 35.0% had DPN alone and 6.0% had DR alone which was comparable to our study findings except for retinopathy (22.7%) which was slightly higher in our study.[7]

Gokhale VS et al., also has reported the studies which investigated the nerve cell damage in retina by Mizutani M et al., and Brownlee M establishing the biological plausibility of complications in relation to diabetes.[9]

In the current study the mean age of those with DR (≈ 57 yrs) was similar to those without DR(≈ 55 yrs) which were not significantly different from Gokhale VS et al., that noted the mean age of 55.3 years among those with DR and 58.3 years among those without.[9]Also similar to the current study on sex-wise distribution, a male preponderance was seen that is 72.7% males. In our study, the duration of diabetes was significantly higher among those with DR (≈ 12 yrs) compared to those with no DR (≈ 7 yrs) and Gokhale VS et al. also demonstrated this with a significant positive correlation[9].

Raman R et al., also found gender (men being at greater risk), longer duration of diabetes as significantly associated history based variables with DR.[17]Rema M et al., in their study, also reported that for every 5 years increase in duration, risk of DR increased by 1.89%[18].

Bansal D et al., and Gill HK et al., have reported age and duration as associated factors with DPN, which are in contrast to this current study finding. However, gender association was not reported in Bansal D et al,.[12,19] The difference may be due to the various factors which play a role viz., status of glycemic control, presence of dyslipidemia, smoking status, delay in the early detection.[20,21] The mean age

of those with DPN as reported by Bansal D et al., was 57 yrs which was in correspondence with our study finding wherein it was 56 yrs.[12]

The prevalence and association in this study are inferred from tertiary hospital based cases, more meaningful outcome can be drawn by undertaking similar studies across the community.

CONCLUSION

More than half of the people with diabetes had diabetic retinopathy (54.0%) and diabetic peripheral neuropathy (50.8%). 57.8% of those with diabetic retinopathy had diabetic neuropathy and 60.1% of those with diabetic neuropathy had diabetic retinopathy. The proportion of people with diabetic peripheral neuropathy (61.6%) among the patients having diabetic retinopathy were significantly higher compared to those with no neuropathy (46.2%). The odds ratio revealed 2 times significantly higher probability of coexisting neuropathy among those with diabetic retinopathy. Among age, gender and duration of disease, diabetic retinopathy was significantly associated with males and long duration of disease however none were observed to be significantly associated with diabetic peripheral neuropathy. Hence we can conclude a higher risk of association of diabetic peripheral neuropathy and diabetic retinopathy. In patients with DPN the screening of DR and vice versa is necessary for their early detection and intervention to prevent these diabetic micro-vascular complications.

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