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A PROSPECTIVE STUDY OF PREVALENCE AND ASSOCIATION OF PERIPHERAL NEUROPATHY IN INDIAN PATIENTS WITH NEWLY DIAGNOSED TYPE 2 DIABETES MELLITUS.

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ABSTRACT

Background: Diabetic peripheral neuropathy (DPN) predisposes to foot ulceration and gangrene. It has been reported that DPN is lower in Indians relative to Caucasians. Studies among recent onset patients with type 2 diabetes mellitus (T2DM) are very few. We studied the prevalence and risk factors of DPN in patients with newly diagnosed T2DM. Individuals with diabetes have reduced HRQoL compared with those without diabetes in the same age group and their HRQoL decreases with disease progression and complications. **Materials and Methods:** We prospectively studied 80 consecutive patients over age 30 with a duration of diabetes ≤1 year. All underwent a clinical and biochemical evaluation and were screened for DPN using TCSS scale (Toronto clinical scoring system) and Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale. Health related QOL questionnaires like the individual EQ-5D dimensions and the EQ-5D index was used to obtain the data regarding the impact of Diabetic Neuropathy complication on the patient's quality of life. **Results:** The cases had a mean age of 60.28 years and duration of symptoms of DM is 1 year prior to presentation. The overall prevalence of DPN was 12.5%. The prevalence of DPN showed an increasing trend with FBS (trend chi-square= 3.517, *P* = 0.0304). A logistic regression analysis showed that DPN was independently associated with Fasting Blood Sugar (*P* = 0.0304), Body mass index (P= 0.0389), HbA1c (*P* = 0.0451), family history (P= 0.0426) and physical activity (P= 0.0219) but not with age, sex and education. **Conclusions:** Our study showed high prevalence

of PN in recently diagnosed patients with T2DM, which was independently associated with age and duration of symptoms of diabetes prior to the diagnosis. FBS, HbA1c, BMI, family history, physical activity were found to be risk factors for prevalence of Diabetic Neuropathy. Patients with Neuropathy also experience negative impact on QOL in many aspects such as mobility, self-care, pain, anxiety and usual activities. Screening for DPN at diagnosis of diabetes is warranted, especially among older subjects.

KEYWORDS: Diabetic Peripheral Neuropathy, Newly Diagnosed, Type 2 Diabetes Mellitus, Quality of Life.

INTRODUCTION

India has one of the highest prevalence of type 2 diabetes mellitus (T2DM) in the world.[1] It is estimated that by the year 2030 there are will be nearly 80 million Indians with T2DM in the country.[2],[3] The disease constitutes a substantial burden for both the patient and health care system, mainly due to macrovascular and microvascular complications.[1],[2] In contrast to patients in industrialized countries, Indians with T2DM have an earlier age at onset of the disease and fewer resources for achieving optimal metabolic control, potentially predisposing higher prevalence of complications.[4],[5],[6]

The prevalence of diabetic peripheral neuropathy (DPN) varies greatly in different studies, ranging from 8% to 59%.[7],[8],[9],[10] DPN significantly increases the risk of complications such as foot infections, deformities, gangrene, and amputations.[11] In India, the adverse effects of peripheral neuropathy (PN) are compounded by poor foot hygiene, improper foot wear, and frequent bare foot walking. In such circumstances, complications of foot infections and gangrene are a common cause of hospital admissions.[1],[12]

T2DM is characterized by a long asymptomatic phase (ranging from 4 to 7 years) between the actual onset of hyperglycemia and clinical diagnosis which may explain the relatively high prevalence of microvascular complications in newly diagnosed patients with T2DM.[13] The prevalence of DPN at diagnosis of type2DM ranges from 10% to 48%, depending upon the population studied and method used to evaluate neuropathy.[14],[15],[16] In view of the poor awareness and lack of regular screening programs, the initial presentation to the physician is frequently delayed. This may predispose to an increased rate of microvascular complications at onset. Ethnic differences in the prevalence of various diabetes-related complications have also been documented.[17]

There is a paucity of reports on DPN in Indians. In a study comparing European and south Asian subjects with T2DM in United Kingdom, the prevalence was lower in the latter. However, in surveys in Indian patients, the prevalence has ranged from 26% to 31%.[18],[19] In these studies, no controls were studied. Since PN is present in a significant proportion of healthy individuals, especially among the elderly, this fact needs to be taken into account before ascribing the PN to hyperglycemia.[11],[20],[21]

Its end-stage complications such as foot ulceration and amputation are associated with substantial health care costs, socioeconomic consequences including loss of work time and reduced quality of life.[22] Previous studies have suggested that PDPN has a negative impact on quality of life. Benbow et al. showed that the occurrence of PDPN has an adverse effect on quality of life when compared with a diabetic control group.[23] The present study was planned to determine the prevalence and risk factors for DPN in newly diagnosed Indian patients with T2DM and age-matched controls.

PATIENTS AND METHODS

➢ Patients and controls

Over a period of 6 months (January 2016 and June 2016), we studied 80 consecutive patients with newly diagnosed T2DM. Inclusion criteria included age ≥35 years, Patients willing to co-operate, Patients detected with Type 2 DM recently (within 1 YEAR) and Patients with FBS- > 120 mg/dl, HbAlc- > 6.5%. Patients diagnosed with DM for more than 1 year, Patients with preexisting complication like Diabetic foot, Patients with Type 1 DM, Patients with Gestational Diabetes Mellitus, patients with acute illness or chronic diseases such as leprosy, those with disability and patients taking medications known to impair nerve function were excluded from the study. The protocol was approved by the institutional ethics committee. Informed written consent was obtained from all subjects.

➢ Clinical and biochemical studies

All participants underwent a standardized clinical evaluation. Height was measured using a stadiometer, while weight was recorded with a weighing machine with a beam balance. Waist and hip circumference were measured and mean of two readings was taken for calculating the waist - hip ratio (WHR).

➢ **Screening for peripheral neuropathy and case definition of diabetic neuropathy**

a. Tests were performed in a random sequence among different patients. Patients were screened for DPN using TCSS scale (Toronto clinical scoring system). This scale was used to assess for the presence of painful Peripheral Neuropathy. In short, for TCSS, symptoms like pain, tingling, numbness, weakness, ataxia, upper limb symptoms as symptom score, knee reflex and ankle reflex as reflex score and pin prick, temperature, light touch, vibration sense, position sense as sensory score were taken into account. Scoring was based on symptoms, reflexes, sensory tests. Depending upon the abnormalities, a point of 0 or 1 was given. Score of 0-5= no peripheral neuropathy; 6-8= mild PN; 9-11= moderate PN; 12-19= severe. The TCSS have been previously been validated against electro-diagnostic studies.[24]

b. Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale was used to assess the severity and pain score of the subjects. This pain scale can help to determine whether the nerves that are carrying the pain signals are working normally or not. Scoring was given. Total score (maximum 24) If score < 12, neuropathic mechanisms are unlikely to be contributing to the patient's pain and If score ≥ 12, neuropathic mechanisms are likely to be contributing to the patient's pain.[25]

c. Health related QOL questionnaires was used to obtain the data regarding the impact of Diabetic Neuropathy complication on the patient's quality of life. This is used to describe how diabetes complications influence the health-related quality of life of individuals with diabetes using the individual EQ-5D dimensions and the EQ-5D index. It Includes Mobility, Self-care, Usual activities, Pain/Discomfort, Anxiety/Depression. In this, the respondents indicate levels of health problems on a number of dimensions of health. Level 1 implies no problem, 2 moderate problem, 3 severe problem. DPN was diagnosed if moderate-severe signs with or without symptoms or mild signs with moderate-severe symptoms were present.[26]

➢ **Screening for albuminuria**

Nephropathy was tested in 80 patients. A urine sample was screened for urine albumin. We collected the 24 hour urine sample of the subjects and submitted them to the bio chemistry lab to obtain microalbuminuria report (microalbuminuria strongly predicts development of Diabetic Nephropathy). Microalbuminuria was diagnosed if at least 2 of the 3 samples had

overnight microalbumin concentration of 20-200 µg/min or urine microalbumin/creatinine ratio of 30-300 µg/mg creatinine.[26]

Assays

Urine albumin concentrations were measured by radioimmunoassay (Immunotech, Prague, Czech Republic). Hemoglobin A1c was measured by high pressure liquid chromatography (D10, Biorad, Hercules, CA, USA). Glucose, creatinine, and lipids were measured by an auto analyzer (Bayer RA-XT, Tarrytown, NY, USA) using kits manufactured by the same company.

Statistics

Continuous data have been expressed as mean ± SD and 95% confidence interval (CI) were determined for the variables. The Student's *t*-test was used for comparison of continuous variables if found to be normally distributed while chi-square test was used to compare categorical variables. Variables associated with PN were tested using univariate logistic regression analysis. Variables shown to have a significant association by this analysis were tested by multivariate logistic regression to determine the variables independently associated with PN. A *P* value <0.05 was considered significant. Statistical analyses were performed using the SPSS software package (version 15.0; SPSS Inc., Chicago, IL, USA).

RESULTS AND DISCUSSION

85.1 % of the patients agreed to participate in the study when informed about the purpose and importance of the study.

Table 1 show, on recruitment; the patients newly detected with DM belonged to age group above 60. HbA1c % of most of the patients on recruitment was above 10%. FBS levels of most patients were less than 200 mg/dl. PLBS of most of the patients was seen to be higher than 250 mg/dl. RBS of most of the patients was seen to be above 180mg/dl.

We detected a high frequency of DPN in newly diagnosed patients with T2DM. DPN was independently associated with increasing age and duration of symptoms of diabetes prior to diagnosis. Simple clinical assessment had a high sensitivity and specificity in detecting DPN. In various Caucasian populations, the prevalence of DPN in newly diagnosed T2DM varies widely from 10% to 48%. This may be due to different methodologies employed for detection of neuropathy as well as variability in patient ages and time elapsed before

diagnosis. However, ethnic differences in DPN may also be relevant.[17] Interestingly, it has been previously reported that both DPN and foot ulcers are lower in Indians compared with European Caucasians.

In the current study, Prevalence of Diabetic Neuropathy is 30%. Two earlier studies in Indians have reported on the prevalence of DPN in newly diagnosed T2DM of 19.5% and 29.0%. In the latter study, the prevalence of DPN was measured by NSS and NDS in 100 newly diagnosed T2DM.[27] In a community-based study from Chennai, south India, Pradeepa *et al*. measured the prevalence of DPN using VPT by biothesiometer. The prevalence in newly diagnosed patients was 19.5% and 27.8% in those with known diabetes.[18] However, the frequency of DPN in the subjects without diabetes was not studied.

Prevalence of mild neuropathy was found to be 15%, moderate Neuropathy was found to be 8.75% and severe Neuropathy was found to be 6.25% based on the TCSS and LANSS criteria (Fig 1). High FBS (>200mg/dl), HbA1c (>10%), BMI (>30 kg/m^2), family history, poor physical activity were found to be risk factors for prevalence of Diabetic Neuropathy.

Since PN is found in a proportion of healthy individuals, especially in the elderly, comparison with a matched control group is essential. We noted PN in 30% of age- and sex-matched control subjects, which increased with advancing age. This fact should be taken into account when assessing PN in patients with diabetes.

Monofilament sensation is a measure of protective sensations in the foot and is strongly associated with risk of foot ulceration.[28] The prevalence of impaired monofilament sensation was 6%, considerably lower than that of DPN. This low frequency may be reflective of the fact that the10-g (5.07) monofilament testing is appropriate for the clinical assessment of risk for foot ulceration[28] but not a sensitive means to detect prevalence of neuropathy. In the latter case, a monofilament of 1g or less may be more appropriate.[29]

Previous studies have identified several risk factors for DPN such as age, poor glycemic control, increasing duration of diabetes, gender, height, body mass index, retinopathy, hypertension, smoking, and alcohol consumption.[14],[15],[16],[18] In the current study, FBS, HbA1c, BMI, family history and physical activity were significant risk factors for Diabetic Peripheral Neuropathy. The prevalence of DPN showed an increasing trend with FBS (trend chi-square= 3.517, P = 0.0304). A logistic regression analysis showed that DPN was

independently associated with Fasting Blood Sugar (*P* = 0.0304), Body mass index (P= 0.0389), HbA1c (*P* = 0.0451), family history (P= 0.0426) and physical activity (P= 0.0219) (Table 2). Since elderly patients have other risk factors for foot ulcerations, such as vision abnormalities and vascular involvement, neuropathy screening assumes an even greater importance in this age group. The prevalence of DPN increased with longer prediabetic period, as reflected by duration of symptoms attributable to diabetes.[30] While some earlier studies have also reported similar findings,[31] these have not been confirmed by others.[32],[33] We noted a prevalence of albuminuria of 20% among newly diagnosed T2DM. However, we found no association of DPN with albuminuria, which may be due to low prevalence of albuminuria noted in this study. Alternatively, there are differences in the pathogenesis of the two complications. In previous studies, the association of DPN with albuminuria has been variably present.[16],[34]

Impact of Diabetic Neuropathy on Qol included severe mobility problems in 20.83% of the population under study, self-care problems (8.33%), severe pain (12.5%), anxiety (8.33%), and severe effect on usual activities (8.33%) (Table3).

The strength of our study is that it was a prospective design; patient evaluation was done by a single physician, and the use of both qualitative and quantitative mode of assessment of neuropathy. It has a few limitations; it was clinic based and may not reflect the actual prevalence of DPN in the community. We did not investigate metabolic causes of PN other than diabetes.

Table 1: Anthropometric Measurement Details

PARAMETER		MALES (N = 40)	FEMALES (N = 40)
AGE	< 60 years	16 (40 %)	12 (30 %)
	> 60 years	24 (60 %)	28 (70 %)
HbA1C (%)	< 10 %	8 (20 %)	14 (35 %)
	> 10 %	32 (80 %)	26 (65 %)
FBS (MG/DL)	< 200 mg/dl	24 (60 %)	22 (55 %)
	> 200 mg/dl	16 (40 %)	18 (45 %)
PLBS (MG/DL)	< 250 mg/dl	16 (40 %)	12 (30 %)
	> 250 mg/dl	24 (60 %)	28 (70%)
RBS (MG/DL)	< 180 mg/dl	6 (15 %)	10 (25 %)
	> 180 mg/dl	34 (85 %)	30 (75 %)

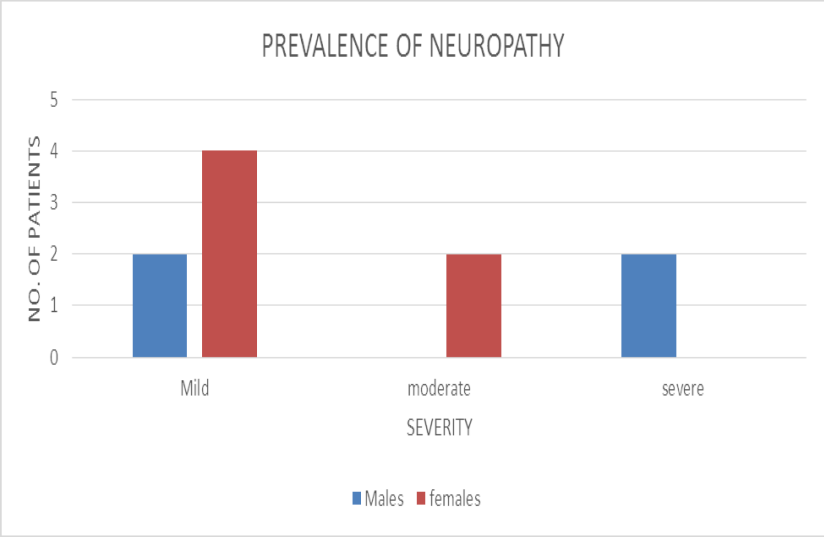

Fig.1: This shows prevalence of Neuropathy as a single complication.

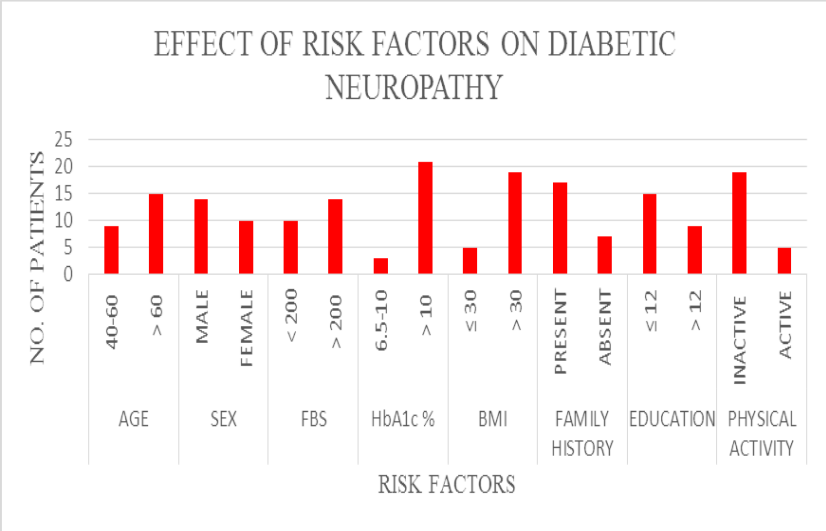

Fig.2: This explains the Effects of Risk Factors on Diabetic Neuropathy.

Table 2: CHI VALUES IN CASE OF DIABETIC NEUROPATHY

RISK FACTOR		COMPLICATION		P VALUE	CHI VALUE
		YES	NO		
AGE (years)	40-60	9	19	0.4796	0.003
	> 60	15	37		
SEX	MALE	14	26	0.1646	0.952
	FEMALE	10	30		
FBS (mg/dl)	< 200	10	36	0.0304	3.517
	> 200	14	20		
HbA1c (%)	6.5 – 10	3	19	0.0451	2.869
	> 10	21	37		
BMI Kg/m^2	≤ 30	5	25	0.0389	3.111
	> 30	19	31		
FAMILY	PRESENT	17	28	0.0426	2.963

HISTORY	ABSENT	7	28		
EDUCATION	≤ 12	15	32	0.3278	0.199
	> 12	9	24		
PHYSICAL ACTIVITY	INACTIVE	19	31	0.0219	4.063
	ACTIVE	5	25		

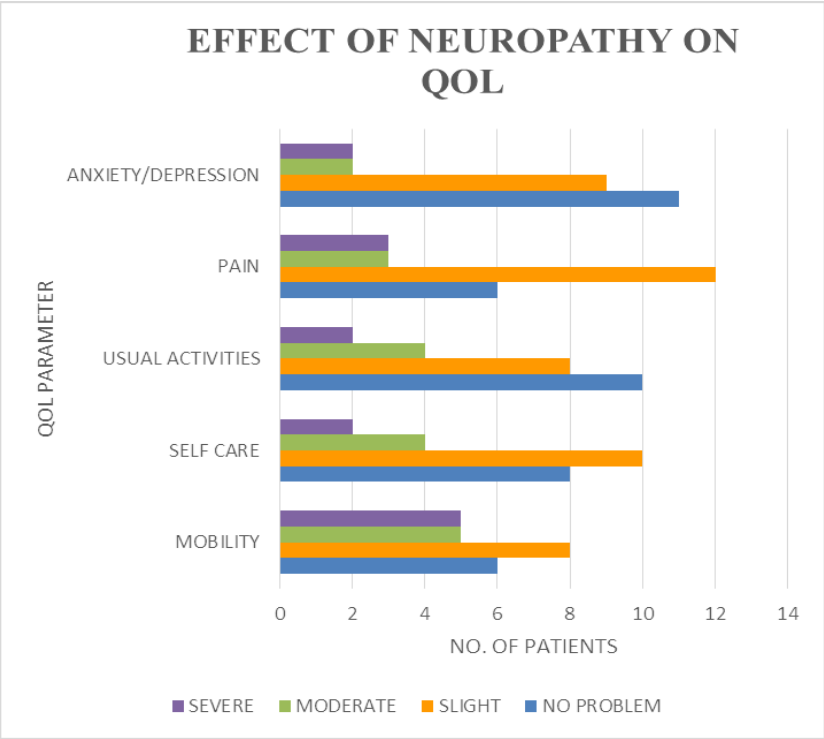

Fig.3: This explains the Effect of Neuropathy on Quality of life.

Table 3: Effect of Diabetic Neuropathy on Quality Of Life

	NO PROBLEM	SLIGHT PROBLEM	MODERATE	SEVERE
MOBILITY	6	8	5	5
SELF CARE	8	10	4	2
USUAL ACTIVITIES	10	8	4	2
PAIN/DISCOMFORT	6	12	3	3
ANXIETY/DEPRESSION	11	9	2	2

CONCLUSION

In summary, we detected a high prevalence of PN in recently diagnosed patients with T2DM. The neuropathy was independently associated with age and duration of symptoms of diabetes prior to the diagnosis. Screening for DPN using simple clinical examination is cost-effective means to prevent foot ulceration and infections in Indian patients with T2DM.

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Conflicts of Interest

No conflicts of interest have been declared.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical Standards of the Institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or Comparable ethical standards.

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