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PREVALENCE OF DIABETIC PERIPHERAL NEUROPATHY (DPN) IN T_2DM HOSPITALIZED PATIENTS: EMERGING TRENDS OF EARLY ONSET, HIGH INCIDENCE AND MORE SEVERE FORM OF DISEASE IN FEMALE PATIENTS

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ABSTRACT

The objective of the study was to investigate the prevalence of Diabetic Peripheral Neuropathy (DPN) in Type 2 diabetes mellitus (T_2DM) patients who were hospitalized due to uncontrolled Hyperglycemia. Details of the patients like age at the diagnosis of DPN, gender, duration of diabetes, and if suffering from hypertension were recorded in order to assess their possible role in the causation of DPN. A total of 100 clinically confirmed T_2DM patients were consecutively selected for the study of which 75 were found to be suffering from DPN while the remaining 25 were negative for Neuropathy. Age of the patient, duration of diabetes and the female gender emerged as the factor to be considered. Important emerging trends recorded in the present study were early age at onset, high preponderance and relatively severe form of neuropathy in female T_2DMpatients.All hypertensive patients were DPN positive indicating the role of hypertension in predisposition to DPN. It is suggested that studies on DPN should be carried out in various ethnic groups and community in view of not only racial differences but also because of differences in their lifestyle and dietary habit. As for the response to neuropathy is concerned, it was observed that mild neuropathy cases responded Optineuron while cases suffering from moderate Neuropathy responded to a combination ofOptineuron with Anti-convulsants. The drug combination prescribed for severe cases of Neuropathy was Venlaflaxine and Optineuron. Additionally, Anti-oxidants and Vitamin B_{12} were prescribed as supplements. Need for studies on the prevalence of neuropathy and its underlying causes are suggested in different ethnic groups taking into account the possible influence of factors like lifestyle, dietary habits and geographical component on incidence. In view of this, the findings in the present study assume significance.

KEYWORDS: *Type 2 Diabetes Mellitus, Peripheral Neuropathy, Hyperglycemia, Hypertension, and Dyslipidemia*

Article History

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INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. The Hyperglycemia is associated with long-term damage, dysfunction and failure of

different organs, especially the Eyes, Kidneys, Nerves, Heart, and Blood vessels. There is an altered metabolism of carbohydrates, lipids, and proteins along with an increased risk of complications from vascular disease (IDF Diabetes Atlas,2013)

Diabetic Peripheral Neuropathy is one of the major microvascularcomplications of T_2DM. The Neuropathy progresses with decreasing nerve functionality and nerve blood perfusion which may result in a malnourished nerve leading to permanent nerve damage (Solomon and Ugoya,2006)

Epidemiology: DPN affects up to 50% of patients with Diabetes. According to the World Health Organization, Diabetic population of the world in 2013 was 382 million and it has been projected to rise to 592 million by the year 2035 (Sandireddy *et al.,* 2014). As a result, the number of patients with DPN will also increase.

Pathophysiology: Hyperglycemia is considered to be a major pathophysiological factor in the development of DPN, the associated mechanisms are not fully understood yet (Schreiber *et al.,* 2015). Some of the major pathways like Polyol Pathway(Nowotny and Grune,2014), Advanced Glycation End Products(Haider *et al., 2014)*, Hexosamine Flux Mitogen-Activated Protein Kinases, altered Activity Of Na+/K+-Atpase (Purves *et al., 2001)*, Poly-ADP Ribose Polymerase (PARP) overactivation, and Cyclooxygenase-2 (COX-2) activation(Rossetti *et al.,*2000) have been reported to play a crucial role in the development and progression of DPN. Nerve cells are prone to hyperglycemic injury as the neuronal glucose uptake is based on external glucose concentration. which is 4-5-fold higher in diabetic subjects. It has been noted in experimental diabetes that the levels of neurotrophic support, including nerve growth factor and insulin-like growth factor, are reduced, which also contribute to malnourishment of nerves. All these pathways form a common platform with the end result as neuronal dysfunction and nerve damage and this translates in the development of various clinical deficits seen in patients suffering from Diabetic Neuropathy. Peroxynitrites which are unstable, structural isomers of Nitrate are formed by the reaction of Hydrogen peroxide with Nitrate also plays an important role in the development of Neuropathy by causing damage to a wide array of molecules in cells including DNA and Proteins(Edwares and Casellini,2015)

Clinical Manifestations:

The Clinical manifestations of DPN includes numbness, burning and tingling sensation. Intractable pain, wounds, and ulcers, Loss of feeling, freezing and Hypersensitivity (Huizinga *et al.,*2007) all these are observed in the distal part of lower limbs.

The Symptoms of DPN are classified as Sensory, Motor, and Autonomic (Akif and Muberrisog, 2015). The symptoms are shown in Figure 1

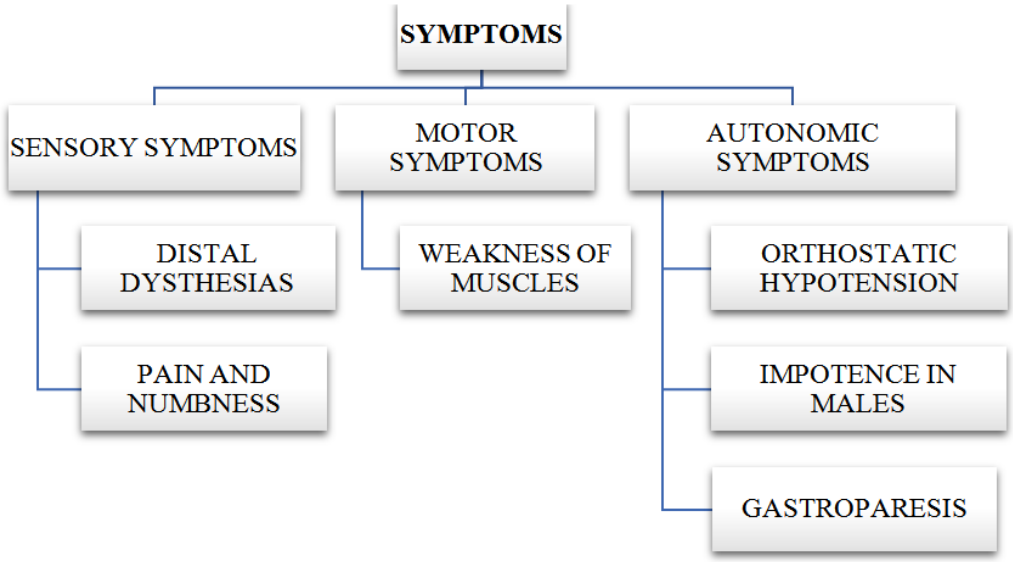

Figure 1: Symptoms of Diabetic Peripheral Neuropathy

The Signs of DPN include Sensory disturbance, Motor signs, and Muscle stretcher flexes (M. Beownlee, 2005). The signs are shown in the Figure 2

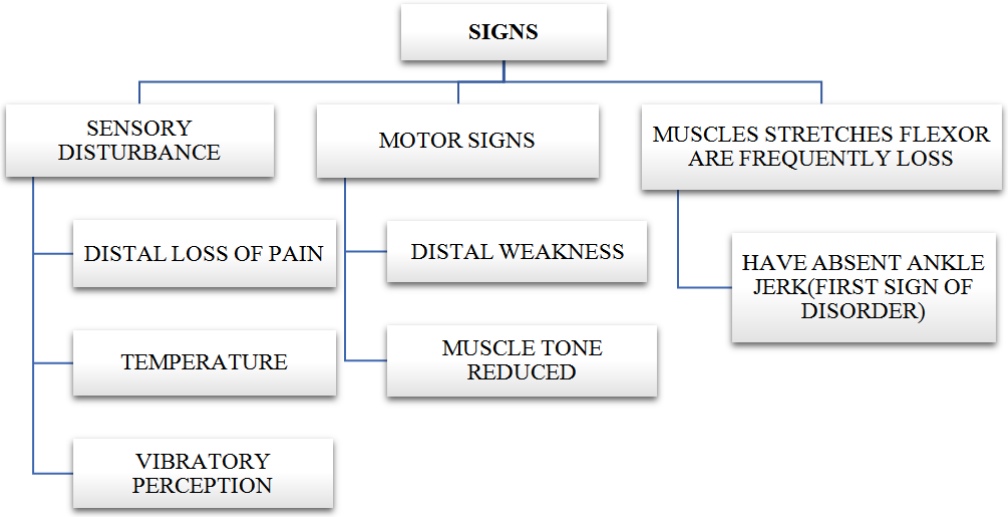

Figure 2: Signs of Diabetic Peripheral Neuropathy

The various drugs used in the treatment of Diabetic Peripheral Neuropathy belong to anti-oxidant and anti-convulsants categories. Some others are used as supplements. Alpha lipoic acids and vitamin C belong to anti-oxidant category (Melham *et al.,2012).* Gabapentin is used as an anti-convulsant while vitamin D and vitamin B complex were used as supplements; Tramadol was used as an Opioid analgesic and Venlaflaxine as a tricyclic anti-depressant(Lippincott 1997)

Despite multimodal and multidisciplinary approaches to the treatment, the primary pathway is pharmacologically based. Three different agents have regulatory approval in the United States for the treatment of DPN: pregabalin, duloxetine, and tapentadol. However, as pain relief is still suboptimal and challenging for clinicians, drugs from various pharmacological classes have been used.

METHODOLOGY

Prior to the initiation of study the Institutional Ethics Committee approval was obtained. A total of 100 clinically confirmed Diabetes Mellitus patients were consecutively selected for the study of which 75 were suffering from Diabetic Peripheral Neuropathy and the remaining 25 were negative for Neuropathy. The diagnosis of DPN was done by using 10-g Semmes-Weinstein Monofilament(Feng *et al.,*2009), 128-Hz Vibration Tuning Fork(Bijli *etal.,2017)* and Toronto clinical scoring system(Udayashankar*et al.,2017)*

The participants were selectedfrom Inpatient and Outpatient department of General Medicine Princess Esra Hospital (DCMS) and the data was recorded in a proforma which consisted of demographic details, diagnosing methods for Neuropathy, anddrug therapy including the Treatment of Neuropathy, Oral Hypoglycemic agents, Antihypertensives and Lipid-Lowering Agents.

RESULTS

The demographic details of the T_2DM patients studied and their base-line clinical characteristics are shown in **Table 1.** It was observed that of the 100 patients recruited in the study the number of cases positive for DPN was 75 while the remaining 25 were devoid of it. Of this 75 DPN positive cases, 29 were males and 46 were females, indicating a higher incidence of DPN among females T_2DM cases. The mean age of the male DPN positive cases was 58 ± 13.4 years compared to 55 ± 11.0 in their female counterparts ($P < 0.05$). All the 75 cases found to be suffering from neuropathy were hypertensive. The mean duration of suffering from T_2DM was comparable between the DPN positive male and female cases (10 ± 5.8 years in males and 9.3 ± 4.5 years in females).

Table 1: Baseline Clinical Characteristics of the Neuropathy Positive and Negative T_2DM Patients

S.No	Base-Line Characters	DPN Positive Case			DPN Negative Cases		
		Males	Females	Total	Males	Females	Total
1	Number of cases	29	46	75	6	19	25
2	Mean age ± S.D (yrs)	58 ± 13.4	55 ± 11.0	-	67.3 ± 16.5	48 ± 14.5	-
3	Duration of DM (yrs)	10 ± 5.8	9.3 ± 4.5	-	9.5 ± 6.5	9.4 ± 4.8	-
4(a)	Hypertensive	29	46	75	-	-	-
4(b)	Non Hypertensive	-	-	-	6	19	25

***P < 0.05**

Table 2: Gender Wise Distribution of DPN Positive Patients According to Class Intervals of Age at Detection of Neuropathy

Class-Interval of Age (Yrs)	Male Patients		Female Patients		Total
	Number	Percentage	Number	Percentage	
21-30	2	6.8%	1	2.2%	3
31-40	3	10.3%	3	6.5%	6
41-50	4	13.4%	13	28.2%	17
51-60	7	24.1%	**16**	34.7%	**23**
61-70	**10**	34.4%	10	21.7%	20
71-80	3	10.3%	3	6.5%	6

Details of gender-wise distribution of DPN positive patients according to class-intervals of age at detection of DPN are given in Table-2. Peak incidence (34.7%) of neuropathy was found to be in female cases in the class- interval 51-60 years in contrast to 61-70 years among male cases indicating early onset of DPN in the female patients. A perusal of

class-interval 41-50 years also reveals a higher percentage of females (28.2%) compared to only (13.4%) in the male patients **(Table 2).**

Apart from age of the patient, the duration of suffering from T_2DM is also considered as an important risk factor for predisposition to DPN. Hence, distribution of male and female DPN positive patients according to duration of (T_2DM) was analyzed **(Table 3).** Longest duration of disease was recorded to be 13.4 years among males DPN positive cases belonging to age group 61-70 years. In contrast to this longest duration of disease (10.6years)was recorded in female patients belonging to class-interval of age 51-60 years. This further supports the contention that in the patients studied in the present study female DPN positive cases have early onset of DPN.

Table 3: Distribution of Males and Females DPN Positive Patients According to the Duration of Diabetes

Class-Intervals of Age (Yrs)	Mean Duration Of Diabetes In Years In Patients	
	Male Patients	Female Patients
21-30	7.5	7
31-40	12	8.6
41-50	8	9.6
51-60	11.2	**10.6**
61-70	**13.4**	8.9
71-80	10.6	7.6

Gender wise analysis revealed a maximum incidence of male Neuropathy cases in 61-70 group while it was highest in 51-60 in female indicating early onset of Peripheral Neuropathy symptoms among female T_2DM patients a decade early. Separately graphs are given for males and females due to variation in Neuropathy

The Distribution of DPN Patients Taking drugs used in the treatment of Neuropathy and Categories Of Neuropathy As Per Toronto Clinical Scoring System is given in **Table-4**

Table 4: The Distribution of DPN Patients Taking Drugs Used in the Treatment of Neuropathy and Categories of Neuropathy as Per Toronto Clinical Scoring System

Category	Total	Vitamin B12	Vitamin B12 + Anti Convulsants	Anti Oxidants + Anti Convulsants	Combinations
Mild	15	10	-	-	5
Moderate	58	-	46	4	8
Severe	2	-	-	-	2

The Combination of Drugs Includes

- Duplex forte + Optineuron.
- Optineuron + Benefit+ Pregabalin
- Gabapentin + Neurobion
- Pregabalin + Optineuron + Vitamin D
- Optineuron + Benefit +Gabapentin
- Optineuron + Benefit +Venlaflaxin
- Neurobion +Pregabalin
- Gabapentin + Vitamin B12

- Optineuron + Bento H
- Venlaflaxin + Duloxetin

The relative proportion of Male and Female DPN positive hypertensive cases in terms of severity (Mild, Moderate and Severe) is shown in **Figure 3.**

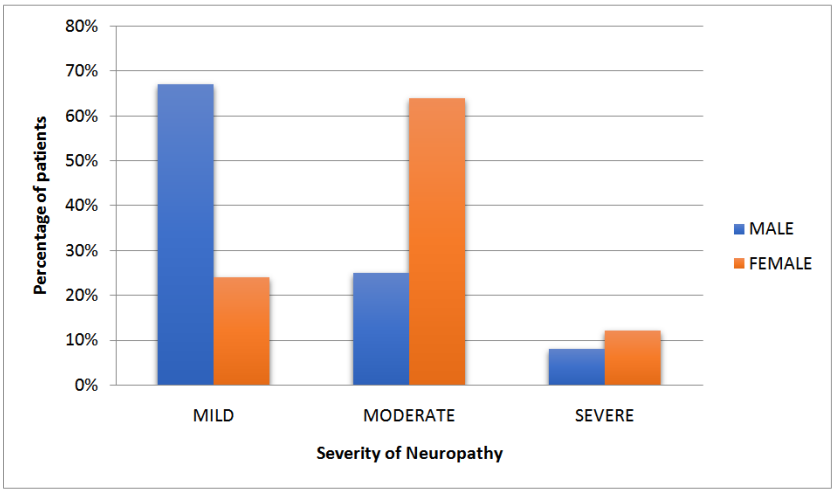

Figure 3: Relative Proportion of Male and Female DPN Positive Hypertensive Cases in Terms of Severity

DISCUSSIONS

In the present study, it was found that Age, Gender, Duration of Diabetes along with Hypertension appeared to be an important risk factor for neuropathy. Most of the studies published on this aspect have not indicated Gender as an important factor for Neuropathy. A significant proportion of female patients suffered from moderate to severe as compared to their male counter parts on the contrary, a large proportion of male cases were identified as suffering from mild DPN.

The high incidence, early age at onset and more severe form of neuropathy observed in the female patients in the present study may be attributed relative sedentary lifestyle and less physical activity.

The prevalence of DPN in diabetic population out of 100 subjects studied was found to be 75%. Gender wise analysis of patients revealed that there is a high preponderance of Females (61%) and that of males (39%). Our findings suggest that if Neuropathy is mild, the patients were given Optineuron if it is moderate, then optineuron and anticonvulsants like pregabalin and gabapentin were given and cases of severe Neuropathy were given venlafaxine and optineuron. The combination drugs were given if additional drug therapy is needed.

Hypertension plays an important role in the progression of Neuropathy as it causes thinning of Myelin sheath. All DPN positive patients were hypertensive. The total percentage of patients diagnosed with mild, moderate and severe neuropathy was 21%, 65%, and 14% respectively. ARB's are potent vasodilators and also helps in the production of reactive oxygen species. We found that the incidence of DPN is more in patients taking ARB's than others.

In this study, the percentage of patients taking oral hypoglycemic agents were diagnosed with mild, moderate and severe neuropathy were 23%, 68%, and 9% respectively. Metformin is a widely prescribed a drug in Diabetic Peripheral Neuropathic patients.

CONCLUSIONS

The Study revealed that the age of the patients and duration of diabetes play an important role in the development of diabetic peripheral neuropathy. Oral Hypoglycemic agents' frequencies are same in cases who are DPN positive and negative. The occurrence of DPN in cases of chronic diabetes could be due to intermittent, indiscipline usage of drugs and could also be due to uncontrolled Hyperglycemia because of their non-compliance to approach Doctor to get the additional combination for better glycemic control. We found that long duration of the disease also predisposes to DPN despite patients are on oral Hypoglycemic agents. It is assumed that Statins may decrease the occurrence of Neuropathy in Diabetic patients as they are known as Lipidlowering agents besides fats are the raw materials for the production of reactive oxygen species, but we found that Neuropathy developed in patients despite taking Statins. Age of patient is an important predisposing factor for Neuropathy. With advancing age the incidence and severity of DPN increases. Surprisingly, 51-70 years of agehas more cases of severity. It appears that Hypertension is an important manifestation in neuropathy cases as it is a risk factor for neuropathy. Among hypertensive DPN population, predominant number was using ARBs for controlling systolic blood pressure and diastolic blood pressure followed by CCBs. The percentage of cases with Severe DPN was 11.7% in those who were taking ARBs while it was only 5.5% in those patients who were on CCBs. Non-hypertensive cases out of 24, 8 were having mild and 16 were moderate none of them were having severe neuropathy as accessed by Toronto clinical scoring system. In view of the high proportion of female cases, it is inferred that females with T_2DM patients are at the high risk of developing DPN

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