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Prevalence & Risk Factors of Peripheral Neuropathy Among Type 2 Diabetic Patients at a Tertiary Care Hospital-a Cross Sectional Study

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Prevalence & risk factors of peripheral neuropathy among type 2 diabetic patients at a tertiary care hospital-A cross sectional study

ABSTRACT

Introduction: Diabetic peripheral neuropathy (DPN), a chronic complication of type 2 diabetes mellitus patients leads to an increased chance of diabetic foot ulcer and lower limb amputation. This study was aimed to find out the prevalence and risk factors of Peripheral Neuropathy among type-II Diabetic patients visiting a tertiary care hospital.

Methodology: A cross-sectional study was conducted among 273 type-II diabetics of either sex attending a General Medicine OPD of tertiary care hospital. A questionnaire with socio-demographic details, anthropometric details, clinical and laboratory parameters and Toronto clinical scoring system for detecting peripheral neuropathy, was administered to each participant.. Data were expressed as mean ± standard deviation for continuous variables and as percentages for categorical variables. Continuous variables were analysed by using student unpaired t test and categorical variables were analysed by using Pearsons chisquare test. The association of risk factors with the prevalence of Diabetic peripheral neuropathy was analysed. The accepted level of significance was set below 0.05 ($P<0.05$).

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Results: Our study consists of a total of 273 type-II Diabetes patients, with 142 males and 131 females. The Prevalence of peripheral neuropathy in our study was found to be 45.4%. male gender, advancing age, increased BMI, longer duration of diabetes, poor glycemic control, Hypertension, increased serum triglycerides & total cholesterol, dyslipdemia, & smoking were found to be significantly associated with the presence of DPN

Conclusion: This study showed that there is a high prevalence of peripheral neuropathy among type-II diabetic patients. Early detection through routine screening and regular follow up examinations will be helpful in preventing the progression of Neuropathy.

Key words: Diabetic peripheral neuropathy (DPN); Risk factors; Toronto clinical scoring system (TCSS)

INTRODUCTION:

International Diabetes Federation has estimated that there were 463 million people with diabetes worldwide in 2019 and is predicted to increase by 2045 to 700 million [1]. India is one of the 7 countries of the IDF SEA region and 88 million people of SEA region have diabetes and is predicted to increase by 2045 to 153 million and there were over 77 million DM patients in India in 2019. [2]. Diabetes mellitus can cause both vascular (micro and macrovascular) and non-vascular complications. Diabetic peripheral Neuropathy is one of the leading cause of non-traumatic lower limb amputation [3].

Diabetic Peripheral Neuropathy (DPN) is defined as the presence of peripheral nerve dysfunction in people with diabetics after exclusion of other causes [4]. Diabetic Peripheral neuropathy involving sensory nerves may don't have symptoms or may have symptoms like numbness, paraesthesia or burning pain in the hands and/or feet [5]. As a result of peripheral neuropathy, when a foot becomes insensate, it is predisposed to the occurrence of neuropathic ulcers which are a leading cause of limb amputation [6]. Thus, early identification of high-risk population is very important so that rigorous modification of risk factors could be initiated before or at early stage of neuropathic process, to reduce further complications and to initiate appropriate intervention.

Nerve conduction study (NCS) is the gold standard test for the diagnosis of Peripheral Neuropathy. But it is cumbersome and expensive and not widely available [7]. So, a clinical scoring system which can be easily performed and that correlates well with NCS, is required. The TCSS is a clinical scoring system introduced by Bril V and Perkins B, and has been found to have a significant correlation with sural nerve myelinated fiber density in patients with diabetic neuropathy [8]. In India it has been validated by D uday Shankar et al. [9].

Identification of diabetes with peripheral neuropathy and its associated factors is the key to reduce further complications and to initiate proper interventions. Hence the present study was aimed to assess the prevalence of peripheral neuropathy based on TCNS score and its associated risk factors among type-II diabetes visiting a tertiary care hospital.

Materials and Methods:

Study design: The study was cross sectional hospital based observational study

Ethics approval: The study was approved by the Institutional ethics committee and informed consent was obtained from the study participants.

Locus of study: General medicine OPD, Viswabharathi Medical College and General Hospital, Kurnool.

Study period: December 2019 to November 2020.

Inclusion criteria: Type-II DM patients with ≥ 3 years of duration of both the sexes aged between 35-80 years were included in the study

Exclusion criteria: Patients with history of Type-I diabetics & taking lipid lowering drugs, Pregnant women/ women who had gestational diabetes, presence of foot ulcers and amputations, and participants with other known causes of peripheral neuropathy

Sampling technique: Purposive sampling technique

Sample size estimation: A sample size of 273 was calculated based on the prevalence of diabetic neuropathy to be 19% from a study done by Ashok S et al. [10] in South India with an absolute precision of 5% and 10% non-response rate using the formula $4pq/d^2$.

Data collection:

A questionnaire which included socio-demographic details such as age, sex, anthropometric details such as height, weight & BMI; smoking & Hypertension history; clinical and laboratory parameters such as Blood pressure, HbA1c, serum cholesterol, serum triglycerides, and Toronto clinical scoring system (TCSS) [8] score for detecting peripheral neuropathy were administered to each participant.

BMI: Participants weight and height readings were taken by using SECA height & weight measuring instrument and Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Hypertension history: Participants was measured on the right arm in the sitting position using mercury sphygmomanometer and considered to be hypertensive if SBP ≥140 mm Hg or DBP ≥ 90mm Hg or taking anti hypertensive treatment. [11]

Bio-chemical analysis: 5 ml of venous blood sample was collected after 8-12 hours overnight fasting. HbA1c, serum triglycerides and serum cholesterol measured. Analysis for serum total cholesterol and triglycerides was done on Stat Fax 3300 semi auto analyzer by enzymatic (CHOD-PAP) colorimetric method [12] and triglyceride by enzymatic (GPO-PAP) method.[13] Dyslipidemia was considered if total cholesterol was ≥ 200 mg/dl and total triglycerides ≥ 150mg/dl. [14]. Analysis for HbA1c was done on Robonik Prietest semi analyser by Immunoturbidimetric latex method. [15]

Diabetic peripheral neuropathy: Participants were screened for DPN using TCSS scale (Toronto clinical scoring system). Scoring was based on symptoms, sensory tests & reflexes. Depending upon the abnormalities, a point of 0 or 1 was given for symptoms and sensory tests

and a point of 0, 1 or 2 was given for reflexes. Total score ranges from 0 to 19. Six points are derived from symptoms, eight from lower limb reflexes, and five from sensory examination distally at the toes. Components of the scale are Foot symptoms scores-Pain, Numbness, Tingling, Weakness and Ataxia. Upper-limb symptoms, reflexes-Knee reflexes and Ankle reflexes and sensory testing-Pinprick, Temperature, Light touch, Vibration and Position.

Severity of neuropathy was classified based on the score as: Score of 0-5= no peripheral neuropathy; 6-8= mild PN; 9-11= moderate PN; 12-19= severe. [8]

Statistics:

Data analysis was done by using Software Package of Social Sciences (SPSS) trial version 16.

Data were expressed as mean ± standard deviation for continuous variables and as percentages for categorical variables. Continuous data were analysed by using student unpaired t test and categorical variables were analysed by using Pearsons chi square test. The association of risk factors with the prevalence of Diabetic peripheral neuropathy was analysed. The accepted level of significance was set below 0.05 ($P<0.05$)

Results:

A total of 273 type-II diabetes mellitus participants including 142 (52%) male patients and 131(48%) female patients were selected into the study. The Characteristics of participants were described in Table-1

TABLE 1 : Characteristics of participants

variable	Mean ± SD	category	frequency	Percentage (%)
Sex	-	Male	142	52
		Female	131	48
Age (Years)	54.75±9.65	<40	16	6
		40-49	69	25
		50-59	101	37
		60-69	70	26
		≥70	17	6
SBP (mm hg)	129.70±16.68	-	-	-
DBP (mm hg)	81.91±9.98	-	-	-
Hypertension	-	Present	111	41
		Absent	162	59
		<18.5	6	2

BMI (kg/m^2)	25.42±4.05	18.5-24.9	130	48
		25-29.9	98	36
		≥30	39	14
HbA1c (%)	6.12±0.57	≤6.5	212	78
		>6.5	61	22
Duration of diabetes (years)	7.41±3.38	<6	101	37
		6-10	128	47
		>10	44	16
Serum cholesterol (SC) (mg/dl)	186.71±38.85	<200	191	70
		≥200	82	30
Serum triglycerides (ST) (mg/dl)	136.68±22.58	<150	221	84
		≥150	52	16
Dyslipidemia	-	Absent	179	65
		Present	94	34
Smoking	-	Present	76	28
		Absent	197	72

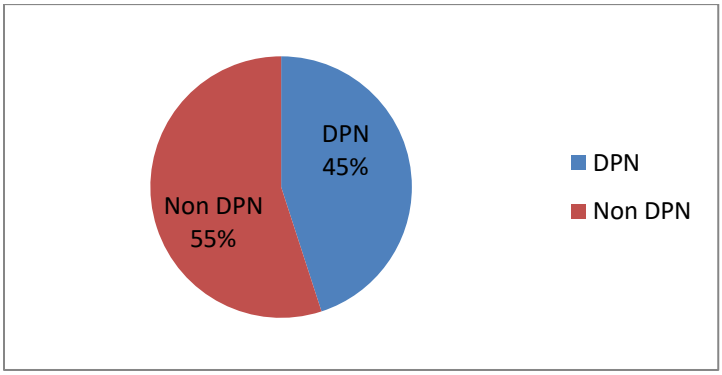
Majority were aged between 50-59 yrs (37%). The mean age of participants was found to be 54.75±9.65. The mean duration of diabetes of participants was found to be 7.47±3.5. The mean BMI of study participants was found to be 25.42±4.05. The mean serum cholesterol of the participants was found to be 186.71±38.85. The mean serum Triglycerides of the participants was found to be 136.68±22.58. The prevalence of hypertension, Smoking & dyslipidemia among the study participants was 41%, 28%, 34% respectively. 22% of study participants were having HbA1c more than 6.5 & 50% of the study participants were having abnormal BMI.

Prevalence and severity of DPN were described in table 2 , table 3, fig 1 & fig 2

TABLE:2 Prevalence of DPN

DPN	Frequency	Percentage
Yes	124	45.42
No	149	54.58
TOTAL	273	100

FIG 1: Prevalence of DPN

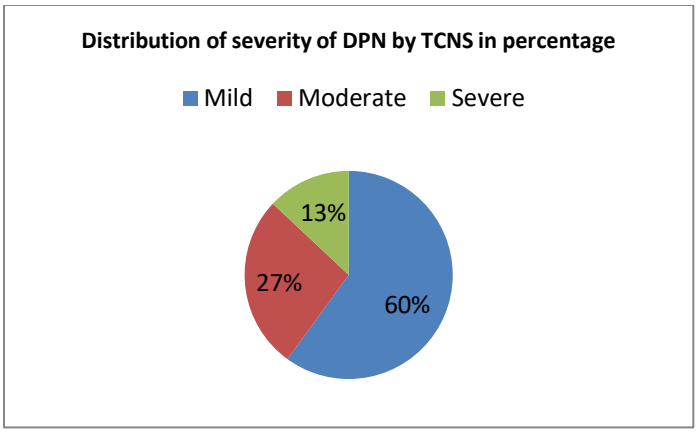


Based on TCSS, the Prevalence of DPN was found to be 45.42% (124/273)

TABLE: 3 **Severity of DPN**

DPN	Frequency	Percentage (%)
Mild	74	60
Moderate	33	27
Severe	17	13
Total	124	100

Fig:2 Severity of DPN



Out of 124 T2DM participants with Peripheral Neuropathy, 60 % individuals had 'Mild', 27% had 'Moderate' and 13% had 'Severe' Peripheral Neuropathy.

The Comparison of continuous variables between DPN & NON DPN participants was described in table 4

Table 4: Comparison of continuous variables between DPN & NON DPN participants

Demographic variable		DPN positive Patients (n=124)	DPN Negitive Patients (n=149)	P value
Age (years)	Mean±sd	57.47±9.67	52.59±8.91	p< 0.001*
BMI (kg/m^2)	Mean± sd	27.81±3.42	23.43±3.42	P< 0.001*
Duration of Diabetes (years)	Mean± sd	8.63±3.70	6.52±3.02	P< 0.001*
HbA1c (%)	Mean± sd	6.53±0.42	5.79±0.44	P< 0.001**
SBP (mm hg)	Mean± sd	133.65± 16.75	126.43± 15.94	P< 0.001*
DBP (mm hg)	Mean± sd	83.89 ±10.21	80.27± 9.54	P<0.05
Serum cholesterol	Mean± sd	201.32± 41.68	174.56 ±31.66	P< 0.001*

(mg/dl)				
Serum triglycerides (mg/dl)	Mean± sd	141.30 ±25.55	132.85 ±19.03	P<0.05

* Significance

** Highly significance

Participants with DPN had high means of Age, BMI, duration of diabetes, serum triglycerides, serum cholesterol and HbA1c compared to those without DPN which are highly significant ($p<0.001$). Participants with DPN had high means of ST & DBP compared to those without DPN which are significant ($p<0.05$)

The association of risk factors with the prevalence of DPN was described in Table 5

Table 5: Association of risk factors with the prevalence of DPN

Demographic variable		DPN Positive	DPN Negative	Total	P value
age	<40	0 (0%)	16 (100%)	16	P<0.001*
	40-49	29 (42%)	40 (58%)	69	
	50-59	44 (43.6%)	57 (56.4%)	101	
	60-69	37 (52.9%)	33 (47.1%)	70	
	≥70	14 (82.4%)	3 (17.6%)	17	
Gender	female	50 (38.2%)	81 (61.8%)	131	
	male	74 (52.1%)	82 (47.9%)	142	P<0.05*
BMI (kg/m^2)	<18.5	0 (0%)	6 (100%)	6	
	18.5-24.9	28 (21.5%)	102 (78.5%)	130	P< 0.001**
	25-29.9	65 (66.3%)	33 (33.7%)	98	
	≥30	31 (79.5%)	8 (20.5%)	39	
Duration of Diabetes	<6	31(30.7%)	70 (69.3%)	101	
	6-10	60 (46.9%)	68 (53.1%)	128	P< 0.001**
	>10	33 (75%)	11 (25%)	44	
HbA1c (%)	<6.5	54 (27.8%)	140 (72.8%)	194	P< 0.001**
	≥6.5	70 (88.6%)	9 (11.4%)	79	
Hypertension	nonHypertensives	54 (33.3%)	108 (66.7%)	162	P< 0.001**
	hypertensives	70 (63.1%)	41 (36.9%)	111	
Serum triglycerides (mg/dl)	<150	86 (38.9%)	135 (61.1%)	221	
	≥150	38 (73.1%)	14 (26.9%)	52	P< 0.001**

Serum cholesterol (mg/dl)	<200	62 (32.5%)	129 (67.5%)	191	P< 0.001**
	≥200	62 (75.6%)	20 (24.4%)	82	
dyslipidemia	absent	52 (29.1%)	127 (70.9%)	179	P< 0.001**
	present	72 (76.6%)	22 (23.4%)	94	
Smoking	Non Smokers	62 (31.6%)	134 (68.4%)	196	P< 0.001**
	smokers	62 (80.5%0	15 (19.5%)	77	

* Significance

* * highly significance

In the present study, increased age, Male gender, duration of DM, HbA1c, BMI, Serum total Cholesterol, serum triglycerides, Dyslipidemia, Hypertension & smoking were found to be significantly associated with peripheral Neuropathy among the type-II diabetic patients. Among these risk factors gender is significant and remaining are highly significant with the presence of DPN among the type-II diabetes.

DISCUSSION:

As diabetic peripheral neuropathy is leading to foot ulcer and amputation, it is important to choose a fast, accurate & inexpensive tool for diagnosing DPN. Very few studies have reported the usage of TCSS in diagnosing DPN. In this study we evaluated the presence of DPN in type-II diabetic patients using TCSS and determined the association of risk factors with DPN. The prevalence of DPN in our study was found to be 45.6%. The estimates of DPN prevalence vary widely from 9.6 to 78% in different populations [16–18] [19–30]. This could be attributed to different types of diabetes (e.g., type 1 and type 2 diabetes), genetic predisposition, age of onset of diabetes, existing health- care facilities, sample selection, different diagnostic criteria used (pin-prick perception, clinical signs and symptoms, and quantitative sensory tests or electrodiagnostic tests) [19] [31–34]

In the present study, we found that males are having the DPN more than the females and it is statistically significant with similar study [35] showing that males being at higher risk in the Diabetes Control and Complications Trial. This was also consistent with the Byron M. Perrin et al. study, [36] which showed Males are more associated with higher risk. Men tend to seek access to health services less than females, perceive that they have less time for their own health and will engage in fewer health-promoting activities [37]

In the present study, BMI was found to be associated with DPN. This was similar to the Braffett BH et al.[38] study which found that great weight and BMI are significantly associated with DPN. nerve damage can be due to chronic metabolic inflammation because of fat deposition, extracellular protein glycation, mitochondrial dysfunction, oxidative stress and activation of counter-regulatory signaling pathways [39-41]

HbA1c was found to be associated with DPN in this study, which was also proved by. Muhammed Umer Nisar etal study [42] which found that Patients with an HbA1c > 6.5% were 16.9 times more likely to develop neuropathy. Poor glycemic control can cause nerve damage and neuronal ischemia [43]

Age & Duration of diabetes were found to be significantly associated with DPN in this study, which was also found similarly by Adler et al. [44] Tefsaye et al., [45] in their studies. Peripheral neuropathy is a chronic complication of diabetes, and takes time to develop. And so it is expected that the older a person with diabetes, there is a possibility of developing DPN, and the longer the duration of diabetes, the risk of complications increases and it will be more if glycemic control is poor and there is more likely the possibility of developing peripheral neuropathy.

In our study Dyslipidemia along with higher triglyceride level & higher LDL-Cholesterol were found to be associated with DPN. Similarly Katulanda P et al. [45] in their study found higher levels of triglycerides as the predictor of DPN and Shiro Tanaka et al [46] in their study predicted that higher LDL Cholesterol is associated with DPN. Companion studies *in vitro* have found that hyperlipidemia in conjunction with hyperglycemia may increase oxidative stress in dorsal root ganglion neurons, leading to mitochondrial injury and axonal degeneration [47–49].

In our study Hypertension was found to be associated with DPN. Similarly Sendi RA etal. [50] in their study found a strong association between DNP and Hypertension. hypertension may cause peripheral diabetic neuropathy or may exaggerate the complications of peripheral diabetes neuropathy as it reduce density of myelination of peripheral nerves [51]

In our study Smoking was found to be associated with DPN. Similarly van der Velde JHPM et al. [52] in their study found that smoking independently contribute to worse nerve function. cigarette smoke by releasing free radicals could induce cellular oxidative stress in many organs, including the nervous system and blood vessels and there by causing cellular damage.[53],[54]

Conclusions:

In our study the prevalence of diabetic peripheral neuropathy using TCSS was found to be high among T2DM patients and the Peripheral neuropathy cases were found to be mild to moderate severity. Early identification and proper intervention are compulsory among patients with male gender, higher BMI, Hypertension, Dyslipidemia, poor glycemic control & Smoking. There is a need for regular screening in patients with type-II diabetes for early identification and preventing the progression of diabetic peripheral neuropathy.

Bibliography:

1. International Diabetes Federation. IDF (2019). Ninth edition 2019. IDF diabetes atlas 9th edition. https://idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html
2. International Diabetes Federation. IDF (2019). Ninth edition 2019. IDF diabetes atlas 9th edition.https://diabetesatlas.org/upload/resources/material/20191218_144626_sea_factsheet_en.pdf
3. Singh G, Chawla S, Amputation in diabetic patients Medical Journal, Armed Forces India 2006 62(1):36-39
4. Boulton AJM, Gries FA, Jervell JA. Guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy. Diabet Med., 1998; 24: 55-95.
5. Davies M, Brophy S, Williams R, Taylor A(2006). The Prevalence, Severity and Impact of painful Diabetic Peripheral Neuropathy in Type 2 Diabetes, Diabetes Care. 29:1518-1522.
6. Poncelet AN (2003). Diabetic Polyneuropathy: risk factors, patterns of presentation, diagnosis and treatment. Geriatrics. 58:16-18
7. Al-Geffari M, Comparison of different screening tests for diagnosis of diabetic peripheral neuropathy in primary health care setting International Journal of Health Sciences 2012 6(2):127-34.
8. Vera Bril, Bruce Perkins.A. Validation of the Toronto Clinical Scoring System for Diabetic Polyneuropathy. Diabetes Care, 2002; 25(11):2048-2052.
9. D Uday shankar, sarah s premraj, , k mayilananthi, Viswanath naragond, Applicability of Clinical Neuropathy Scoring and its Correlation with Diabetic Peripheral Neuropathy: A Prospective Cross-sectional Study Journal of Clinical and Diagnostic Research. 2017 Dec, Vol-11(12): OC10-OC13
10. Ashok S, Ramu M, Deepa R, Mohan V. Prevalence of neuropathy in type 2 diabetic patients attending a diabetes centre in South India. JAPI. 2002;50:546- 50.
11. A. V. Chobanian, G. L. Bakris, H. R. Black et al., "The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report," e Journal of the American Medical Association, vol.289, no. 19, pp. 2560–2572, 2003.
12. Allain C C, Poon I S, Chan C H G, Richmond W and Fu P C (1974) Enzymatic determination of serum total cholesterol.*Clin. Chem.* **20:** 470-471.
13. Jacobs N J and VanDenmark P J (1960) Enzymatic determination of serum triglyceride.ch.

Biochem. Biophys. **88:** 250-255
14. National Cholesterol Education Program: Detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Circulation. 2002, 106: 3143-3421.
15. F Engbaek, S E Christensen, B Jespersen, Enzyme immunoassay of hemoglobin A1c: analytical characteristics and clinical performance for patients with diabetes mellitus, with and without uremia, Clin Chem. 1989; 35(1): 93-7.
16. Rani PK, Raman R, Rachapalli SR, *et al.* Prevalence and risk factors for severity of diabetic neuropathy in type 2 diabetes mellitus. *Indian J Med Sci* 2010; 64: 51–57.
17. Pradeepa R, Rema M, Vignesh J, *et al.* Prevalence and risk factors for diabetic neuropathy in an urban south Indian population: the Chennai Urban Rural Epidemiology Study (CURES-55). *Diabet Med* 2008; 25: 407–412.
18. Raman R, Gupta A, Krishna S, *et al.* Prevalence and risk factors for diabetic microvascular complications in newly diagnosed type II diabetes mellitus. Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study (SN-DREAMS, report 27). *J Diabetes Complications* 2012; 26: 123–128.
19. Young MJ, Breddy JL, Veves A, *et al.* The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds. A prospective study. *Diabetes Care* 1994; 17: 557–560.
20. Yousif AR. Predicting microvascular complications in diabetic patients. *Iraqi J Med Sci* 2011; 9: 195–205.
21. Morkrid K, Ali L, Hussain A. Risk factors and prevalence of diabetic peripheral neuropathy: a study of type 2 diabetic outpatients in Bangladesh. *Int J Diabetes Dev Ctries* 2010; 30: 11–17.
22. Katulanda P, Ranasinghe P, Jayawardena R, *et al.* The prevalence, patterns and predictors of diabetic peripheral neuropathy in a developing country. *Diabetol Metab Syndr* 2012; 4: 21.
23. Cardoso CR, Salles GF. Predictors of development and progression of microvascular complications in a cohort of Brazilian type 2 diabetic patients. *J Diabetes Complications* 2008; 22: 164–170.
24. Lu B, Yang Z, Wang M, *et al.* High prevalence of diabetic neuropathy in population-based patients diagnosed with type 2 diabetes in the Shanghai downtown. *Diabetes Res Clin Pract* 2010; 88: 289–294.
25. 2Rubino A, Rousculp MD, Davis K, *et al.* Diagnosis of diabetic peripheral neuropathy among patients with type 1 and type 2 diabetes in France, Italy, Spain, and the United Kingdom. *Prim Care Diabetes* 2007; 1: 129–134.
26. Kasim K, Amar M, Sadek AAE, *et al.* Peripheral neuropathy in type-II diabetic patients attending diabetic clinics in Al-Azhar University Hospitals, Egypt. *Int J Diabetes mellitus* 2009; 2: 20–23.
27. Fedele D, Comi G, Coscelli C, *et al.* A multicenter study on the prevalence of diabetic neuropathy in Italy. Italian Diabetic Neuropathy Committee. *Diabetes Care* 1997; 20:

836–843.
28. Abougalambou SS, Abougalambou AS. Explorative study on diabetes neuropathy among type II diabetic patients in Universiti Sains Malaysia Hospital. *Diabetes Metab Syndr* 2012; 6: 167–172.
29. Shaw JE, Hodge AM, de Courten M, *et al*. Diabetic neuropathy in Mauritius: prevalence and risk factors. *Diabetes Res Clin Pract* 1998; 42: 131–139.
30. Gregg EW, Sorlie P, Paulose-Ram R, *et al*. Prevalence of lower-extremity disease in the US adult population >=40 years of age with and without diabetes: 1999-2000 national health and nutrition examination survey. *Diabetes Care* 2004; 27: 1591–1597.
31. Masson EA, Hunt L, Gem JM, *et al*. A novel approach to the diagnosis and assessment of symptomatic diabetic neuropathy. *Pain* 1989; 38: 25–28.
32. Dyck PJ, Kratz KM, Lehman KA, *et al*. The Rochester Diabetic Neuropathy Study: design, criteria for types of neuropathy, selection bias, and reproducibility of neuropathic tests. *Neurology* 1991; 41: 799–807.
33. Tapp RJ, Shaw JE, de Courten MP, *et al*. Foot complications in Type 2 diabetes: an Australian population-based study. *Diabet Med* 2003; 20: 105–113.
34. Bruce SG, Young TK. Prevalence and risk factors for neuropathy in a Canadian First Nation community. *Diabetes Care* 2008; 31: 1837–1841.
35. Factors in development of diabetic neuropathy. Baseline analysis of neuropathy in feasibility phase of diabetes control and complications trial (DCCT). Diabetes 1988;37:476.
36. Perrin BM, Allen P, Gardner MJ, Chappell A, Phillips B, Massey C, et al. The foot-health of people with diabetes in regional and rural Australia: Baseline results from an observational cohort study. J Foot Ankle Res. 2019;12(1):1–9
37. Taylor C, Stewart A, Parker R. 'Machismo' as a barrier to health promotion in Australian males. In: Laws T, editor. Promoting men's health. Melbourne: Ausmed Publications; 1998. pp. 15–31.
38. Braffett BH, Gubitosi-Klug RA, Albers JW, Feldman EL, Martin CL, White NH, et al. Risk factors for diabetic peripheral neuropathy and cardiovascular autonomic neuropathy in the Diabetes Control and Complications Trial/Epidemiology of Diabetes interventions and Complications (DCCT/EDIC) study. 2020;69(5):1000–1010.
39. Callaghan B, Feldman E (2013) The metabolic syndrome and neuropathy: therapeutic challenges and opportunities. Ann Neurol 74: 397-403.
40. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A; KORA Study Group (2008) Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy: the MONICA/KORA Augsburg Surveys S2 and S3. Diabetes Care 31: 464-469.
41. Smith AG, Singleton JR (2013) Obesity and hyperlipidemia are risk factors for early

diabetic neuropathy. J Diabetes Complications 27: 436-442.
42. Muhammed Umer Nisar. Association of Diabetic neuropathy with Duration of Type 2 Diabetes and glycemic control. Curious, 2015 Aug; 7(8): e302.
43. Edwards, J. L., Vincent, A. M., Cheng, H. T., & Feldman, E. L. (2008). Diabetic neuropathy: mechanisms to management. Pharmacology & therapeutics, 120(1), 1-34
44. Adler AI, Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Smith DG(1997). Risk factors for diabetic peripheral sensory neuropathy: Results of the Seattle Prevalence Diabetic Foot Study. Diabetes Care. 20:1162-1167.
45. Tesfaye S, Chaturvedi N, Eaton SE, Ward JD, Manes C, Ionescu-Tirgoviste C, Witte DR, Fuller JH (2005). Vascular risk factors and diabetic neuropathy. N Eng J Med. 352(4):341-350
46. Katulanda P, Ranasinghe P, Jayawardena R, *et al.* The prevalence, patterns and predictors of diabetic peripheral neuropathy in a developing country. *Diabetol Metab Syndr* 2012; 4: 21.
47. Tanaka S, Iimuro S, Yamashita H, *et al.* Predicting macro- and microvascular complications in type 2 diabetes: The Japan Diabetes Complications Study/the Japanese elderly diabetes intervention trial risk engine. *Diabetes Care* 2013; 36: 1193–1199
48. Padilla A, Descorbeth M, Almeyda AL, Payne K, De Leon M. Hyperglycemia magnifies Schwann cell dysfunction and cell death triggered by PA-induced lipotoxicity. Brain Res. 2011;1370(0):64–79.
49. Lupachyk S, Watcho P, Hasanova N, Julius U, Obrosova IG. Triglyceride, nonesterified fatty acids, and prediabetic neuropathy: role for oxidative–nitrosative stress. Free Radic Biol Med. 2012;52(8):1255–63
50. Vincent AM, Callaghan BC, Smith AL, Feldman EL. Diabetic neuropathy: cellular mechanisms as therapeutic targets. Nat Rev Neurol. 2011;7(10):573–83.
51. Sendi RA, Mahrus AM, Saeed RM, Mohammed MA, Al-Dubai SAR. Diabetic peripheral neuropathy among Saudi diabetic patients: A multicenter cross-sectional study at primary health care setting. *J Family Med Prim Care*. 2020;9(1):197-201.
52. Forrest KY, Maser RE, Pambianco G, Becker DJ, Orchard TJ. Hypertension as a risk factor for diabetic neuropathy: a prospective study. Diabetes 1997; 46(4), 665-670.
53. van der Velde JHPM, Koster A, Strotmeyer ES, et al. Cardiometabolic risk factors as determinants of peripheral nerve function: the Maastricht Study. *Diabetologia*. 2020;63(8):1648-1658.
54. Morrow JD, Frei B, Longmire AW, *et al* Increase in circulating products of lipid peroxidation (F2-isoprostanes) in smokers. Smoking as a cause of oxidative damage. N Engl J Med 1995; 332: 1198–1203.
55. Zhou JF, Yan XF, Guo FZ, *et al* Effects of cigarette smoking and smoking cessation on plasma constituents and enzyme activities related to oxidative stress. Biomed Environ Sci 2000; 13: 44–55.