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Peripheral Neuropathy and Cardiac Autonomic Neuropathy among Type II Diabetic Patients: Prevalence and Risk Factors

B. V. Surendra[1*], N. S. Muthiah[2], M. V. Sailaja[3,4] and K. Sreenivasulu[4]

[1]Department of Physiology, Bharath Institute of Higher Education and Research, Chennai, India.
[2]Department of Pharmacology, Balaji Medical College, Chennai, India.
[3]Department of Physiology, Viswabharathi Medical College, Kurnool, India.
[4]Department of Anatomy, Viswabharathi Medical College, Kurnool, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: The two most common chronic complication softype 2 diabetes mellitus (T2DM) are peripheral neuropathy (PN) and Cardiac autonomic neuropathy (CAN).Diagnosing neuropathies at subclinical stage can prevent the morbidity and mortality.
Objectives: To determine the prevalence of peripheral neuropathy and cardiovascular autonomic neuropathy and their risk factors in type-II diabetic patients attending a tertiary care hospital.
Methods: An observational cross sectional study was done from December 2019 to November 2020 in the department of General medicine at tertiary care hospital. 273 type II diabetic patients were selected for this study. Toronto clinical scoring system was used for assessing PN and ewings cardiovascular reflex study was used done to assess CAN. To identify the risk factors of PN and CAN, Logistic regression analysis was used.
Results: The prevalence of PN and CAN was 45.4% and 34.06% respectively, while29.3% participants had both. Smoking (OR: 12.976; 95% CI: 0.052–0.418, P<0.0001) and poor glycaemic control (OR: 27.231; 95% CI: 5.226–38.201, P<0.0001) were independent risk factors of DPN.

**Corresponding author: E-mail: drsurendraphysiology@gmail.com;*

poorglycaemic control (OR: 26.970; 95% CI: 3.507–16.055, *P* <0.0001) and Dyslipidimea (OR: 11.792; 95% CI: 0.096–0.526, *P* ≤ 0.001) were independent predictors of CAN.
Interpretation and Conclusions: PN and CAN are common among diabetic patients, and thus it is recommended to screen Peripheral Neuropathy and CAN in all diabetic patients for the early diagnosis and preventing the debilitating complications

Keywords: Type-II diabetes mellitus; peripheral neuropathy; cardiac autonomic neuropathy (CAN); toronto clinical scoring system (TCSS); ewings tes.

1. INTRODUCTION

Diabetic Neuropathy (DN) is the major cause for hospitalization than other complications of diabetes and is also the most common cause for non-traumatic amputation and autonomic failure [1,2] and thus causing negative effect significantly on quality of life of patientswithT2DM [3]

There are 4 different types of neuropathy: peripheral neuropathy, proximal neuropathy, autonomic neuropathy & focal neuropathy. In peripheral neuropathy the symptoms varies from severely painful at one extreme to the completely painless and the patients having damage to the nerves looses the ability to perceive the sensations like heat, cold and pain in extremities and thus Peripheral Neuropathy participates in causing foot ulceration [4].

In CAN, parasympathetic and sympathetic functions are altered, but still these dysfunctions are masked for longtime. CAN is identified at later stages as autonomic system can react to both internal environment stress and external environment stress [5]. CAN is one of the leading cause of increasing incidence of silent myocardial ischemia and sudden death is in T2DM patients [6-7].

Early screening, appropriate intervention and treatment of Peripheral neuropathy and CAN in T2DM are very important as these two neuropathies are masked and neglected at subclinical stage and ultimately leading to debilitating complications.

The present study was planned to determine the prevalence and risk factors of peripheral neuropathy, Cardiac autonomic neuropathy (CAN) among type-II Diabetes Mellitus participants in a tertiary care hospital.

2. MATERIALS AND METHODS

This cross sectional observational study was done among type II Diabetic patients attending general medicine OPD at Viswabharathi medical college Kurnool from December 2019 to November 2020.

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. [8] in South India with an absolute precision of 5% and 10% non-response rate using the formula 4pq/d2.

The Inclusion criteria are Type II Diabetes mellitus patients aged 35 to 80 years & with ≥ 3years of duration of diabetes.

The Exclusion criteria are Other known causes of peripheral neuropathy, history of patients related to nerve injury, pregnant woman who had gestational diabetes, presence of foot ulcers & amputations, Participants with other diseases associated with autonomic nervous system dysfunction, Patients on drugs like antiarrhythmics, patients with underlying cardiac illness like coronary artery disease, ischemic heart disease, rheumatic heart disease, and cardiac failure,

Sampling technique: Purposive sampling method

All the patients underwent a standardized clinical evaluation

Study protocol: Demographic data such as age, sex. Smoking & hypertension history by using structured questionnaire

BMI: Participants height and weight were measured and Body mass index (BMI) was calculated

Hypertension: blood pressure of the participants was measured in the right arm using mercury column sphygmomanometer after patient had adequately rest and seated and considered to be hypertensive if SBP ≥140 mm Hg or DBP ≥ 90mm Hg or taking anti hypertensive drugs [9].

Biochemical analysis: Five milliliters of venous bloods was drawn under aseptic conditions for serum glycosylated haemoglobin (HB), serum triglycerides& Cholesterol.

Serum total cholesterol and triglycerides was investigated by enzymatic (CHOD-PAP) colorimetric method [10] and enzymatic (GPO-PAP) method [11] on Stat Fax 3300 semi auto analyzer.Dyslipidemia was considered if total cholesterol was ≥ 200 mg/dl and total triglycerides ≥ 150mg/dl [12]. By Immuno turbidimetric latex method [13] HbA1c was investigated on Robonik Prietest semi analyser.

Diabetic peripheral neuropathy: TCSS Scale was used for screening DPN among type-II diabetic patients. Scoring was given for symptoms, sensory tests & reflexes. Based on the abnormalities, for symptoms and sensory tests, a point of 0 or 1 was given and for reflexesa point of 0, 1 or 2 was given. Total score ranges from 0 to 19. Finally, for Symptoms 6 points were given, for sensory examination 5 points were given and for lower limb reflexes, 8 points were given. Components of the scale are:

Foot symptoms scores-Pain, Numbness, Tingling, Weakness and Ataxia. Upper-limb symptoms, sensory testing-Pinprick, Temperature, Light touch, Vibration and Position and reflexes-Knee reflexes and Ankle reflexes

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 [14].

Ewings Cardiovascular Reflex Tests (CRT): All the patients selected for study underwent Cardiovascular Reflex Tests (CRT) for evaluation of Cardiac autonomic neuropathy. Standard 12 lead ECG was taken and heart rate was measured by by continuous ECG recording using lead II. All five Ewing`s tests [15] were performed as following for the detection of DCAN (diabetic cardiac autonomic neuropathy)

Instruments:

1. ECG instrument (CONTEC ECG300G) with paper speed of 25mm/sec
2. Diamond Sphygmomanometer BP instrument

I. Tests for assessing parasympathetic function

1) Heart rate response to deep breathing test:
2) Heart rate response to Valsalva maneuver
3) Heart rate response to standing

II..Tests for assessing sympathetic function:

1) Blood pressure response to sustained hand grip
2) Blood pressurere sponseto standing

The results were then categorized into one of the four groups

- Normal
- Early CAN - One of three parasympathetic tests abnormal or two borderline
- Definite CAN- Two parasympathetic tests abnormal
- Severe CAN- Two parasympathetic tests abnormal + one or both sympathetic tests abnormal

Statistics

Data analysis was done by using SPSS-16.continuous variables were reported as mean ± standard deviation and categorical variables were reported as percentages. Risk factors associated with DPN and CAN were determined using multivariate logistic regression analyses, with results presented as adjusted odds ratio (OR) with corresponding 95% confidence interval(CI).The accepted level of significance was set below 0.05 ($P<0.05$).

3. RESULTS

The characteristics of the study participants were described in Table 1.

The tests of diabetic peripheral neuropathy and cardiac autonomic neuropathy were described in Table 2.

Factors associated with Diabetic peripheral Neuropathy on multivariate analysis were described in Table 3.

Factors associated with cardiac autonomic neuropathy on multivariate analysis were described in Table 4.

4. DISCUSSION

This study estimated the prevalence and risk factors of peripheral neuropathy and CAN among type II diabetic patients attending a tertiary care

Table 1. characteristics of study subjects

Baseline characteristics	Mean±SD	Category	Frequency (n)	Percentage (%)
Sex	-	Male	142	52
		female	131	48
Age	54.75±9.65	-	-	-
Duration of DM (Years)	7.41±3.38	-	-	-
BMI (kg/m^2)	25.42±4.05	-	-	-
SBP	129.70±16.68	-	-	-
DBP	81.91±9.98	-	-	-
HbA1c(%)	6.12±0.57	-	-	-
Serum Cholesterol (mg/dl)	186.71±38.85	-	-	-
Serum Triglycerides (mg/dl)	136.68±22.58	-	-	-
Hypertension	-	absent	162	59
		present	111	41
Dyslipidemia	-	absent	179	65
		present	94	34
smoking	-	absent	197	72
		present	76	28

Table 2. Tests of diabetic peripheral neuropathy and cardiac autonomic neuropathy

9.5	Participants (*n*=273), *n*(%)
DPN	
Present	124 (45.4)
Absent	149(54.6)
Valsalva	
Abnormal 27 (9.9)	
Borderline	82 (30.0)
Normal	164(60.1)
Deep breathing	
Abnormal	58 (21.2)
Borderline	24 (8.8)
Normal	191 (70.0)
HRV to standing	
Abnormal	46 (16.9)
Borderline	45 (16.5)
Normal	182 (66.6)
BP change on standing	
Abnormal	05 (1.8)
Borderline	05 (1.8)
Normal	263 (96.4)
BP change on handgrip	
Abnormal	2 (0.7)
Borderline	7 (2.6)
Normal	264 (96.7)
CAN	
Present	93 (34.0)
Absent	180(66.0)
Type of can	
early	36(38.7)
Definite	51 (54.8)
Advance	6 (6.5)
DPN + CAN	
Present	80 (29.3)
Absent	193 (70.7)

BP: Blood pressure, HRV: Heart rate variability DPN: Diabetic Peripheral Neuropathy, CAN: Cardiovascular autonomic neuropathy

Table 3. Factors associated with Diabetic peripheral Neuropathy on multivariate analysis

95% CI for OR	p			
Variables		Lower	Upper	
OR				
Age ≥60 years	1.638	0.062	1.795	0.201
Male sex	3.163	0.075	0.212	1.078
Duration of diabetes ≥8 years	0.003	0.354	2.995	0.957
Presence of hypertension	1.039	0.308	0.704	3,043
BMI	0.025	0.875	0.260	3.146
Poor glycaemic control	27.231	5.226	38.201	<0.001*
Smoking	12.976	0.052	0.418	<0.001*
Dyslipidmea	0.949	0.265	1.563	0.330

Table 4. Factors associated with cardiac autonomic neuropathy on multivariate analysis

95% CI for OR				
Variables		Lower	Upper	P
OR				
Age ≥60 years	0.097	0.281	5.751	0.755
Male sex	0.034	0.480	2.424	0.854
Duration of diabetes ≥8 years	0.012	0.350	2.554	0.912
Presence of hypertension	1.235	0.726	3.187	0.266
BMI	0.020	0.361	3.247	0.887
Poor glycaemic control	26.970	3.507	16.055	<0.001*
Smoking	0.115	0.314	2.264	0.735
Dyslipidmea	11.792	0.096	0.526	0.001*

hospital in Kurnool. The prevalence of DPN as evaluated by TCSS in this study was45%.Sankari Mansa Devi H et al. [16] in 2015 reported the prevalence of DPN among OPD attendants as evaluated by TCSS as 13.2%. sangeetha et al. [17] in 2019 in their study reported the prevalence of DPN as evaluated by MNSI history version and MNSI examination as 31% & 24%.

Prevalence of CAN in this study was 34%. DAN study in 2014 reported the prevalence of CAN among the type-II Diabetes as 35% [18] & Lerner et al. [19] al in 2015 reported the prevalence of CAN as 37% among type II diabetic patients which are correlating to the present study. Tallat N et al. [20] in 2019 reported the prevalence of CAN as 40%. Gupta and Gupta in 2017 [21] reported prevalence of CAN as 54%.

The results of this study showed that the development of peripheral neuropathy had a significant association with poor glycaemic control. Similar observation was described in a study by bansal et al. [22]. The result of this study showed that Habit of smoking increased the risk of DPN. Similar observation was described in a study by Katulanda P et al. [23].

This study did not find significant association peripheral neuropathy with age, sex, duration of diabetes, hypertension, BMI & dyslipidimea. Smoking [24–26] may increase the risk of nerve damage through oxidative stress, systemic inflammation, and endothelial dysfunction independent of diabetes [24–26], in parallel with metabolic factors.

The results of this study showed that the development of CAN had a significant association with poor glycaemic control. Similar observation was described in a study by Anjum S et al. [27]. The results of this study showed that the development of CAN had a significant association with dyslipdimea. Similar observation was described in a study by Zuern et al. [28].

This study did not find significant association of CAN with age, sex, duration of diabetes, hypertension, BMI &smoking. Even though in clinical trials the association of dyslipidemia with neuropathy is confirmed, the mechanism by which dyslipidmea causes neuropathy is not clear. Of these possibly the most important is,

oxidative stress. Increased oxidative stress can lead to the pathology of neural dysfunction in diabetes and has been proposed as a mechanism that contributes to the pathogenesis of neuropathy [29,30].

In our study it was observed that Patients with poor glycaemic control have about 27 times increase in the risk of developing PN& CAN. Blood glucose levels if consistently high, can lead to macrovascular and micro vascular complications which affect patients quality of life [31]. Hyperglycemia contributes to the activation of various biochemical pathways related to the metabolic state of the cell and along with impaired nerve perfusion, contributes to the development and progression of diabetic neuropathies [32].

5. CONCLUSION

This study showed that PN and CAN are quite common among diabetic patients and with about one in four patients having a mixed form of the two. In the regular examination of Type 2 Diabetes Mellitus patients, these simple noninvasive tests for Peripheral Neuropathy and Cardiac autonomic neuropathy can be incorporated for the early diagnosis of peripheral neuropathy and cardiac autonomic neuropathy to prevent the complications.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

Institutional ethics committee approval was taken for conducting the study and written & informed consent form was taken from all the participants.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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