Original Article

Autonomic Neuropathy in Patients with Diabetic Peripheral Neuropathy: A Cross Sectional Study

Meghana Shridhar[1], Poonam Ashok Kamath[2], Sudha Vidyasagar[3], Pallavi L C[4], Vijayendra Kedage[5]

Abstract

Aims and Objective : The aim of our study was to estimate the proportion of autonomic neuropathy in Diabetes Mellitus patients with peripheral neuropathy. Our objectives were to perform cardiac autonomic neuropathy function tests. As a secondary objective we strived to determine the association of autonomic neuropathy with severity and different types of diabetic peripheral neuropathy and to determine prevalence of autonomic neuropathy in patients with hypoglycemia who present with neuroglycopenia.

Materials and Methods : In a cross-sectional study, 120 patients with diabetic peripheral neuropathy were selected. They were subjected to bedside testing for autonomic neuropathy. Patients who had resting tachycardia and significant postural hypotension were taken up for cardiac autonomic function testing in physiology lab.

Results : Out of 120 subjects, 109 had distal symmetric polyneuropathy, 9 had amyotrophy and 1 subject each had mononeuritis multiplex and mononeuropathy. Out of these subjects, 52% had resting tachycardia and 35% subjects had postural hypotension suggestive of autonomic neuropathy. 63.3% of subjects had autonomic neuropathy, out of which cardiac autonomic neuropathy was found in 41.7% subjects. In 30 patients had documented hypoglycemia out of which 23 had autonomic neuropathy. In 19 patients had neuroglycopenia out of which 17 had severe autonomic neuropathy.

Conclusions : There is a significant association between autonomic neuropathy and diabetic peripheral neuropathy. Hypoglycemia and neuroglycopenia patients were found to have higher predilection to develop autonomic neuropathy.

Key words : Cardiac Autonomic Neuropathy, Resting Tachycardia, Orthostatic Hypotension, Neuroglycopenia.

Diabetes is a disease with vascular repercussions. Of these, peripheral neuropathy is a well-studied microvascular complication, manifesting as Distal Symmetrical Polyneuropathy-sensory and motor (DSPN), plexopathy, mononeuropathy, mononeuritis multiplex and amyotrophy[1].

Various studies done in western population shows a lifetime prevalence of peripheral neuropathy of 50% in individuals with long-standing type 1 and type 2 DM[2]. Review of Indian literature revealed a study done by Darivemula, *et al* in rural areas of Andhra Pradesh, India, in 2017 showed a prevalence of 39.3%[3]. Another study done by D'Souza, *et al* in Mangalore, India in 2014 showed a prevalence of 32.2%[4]. This study used the Michigan scoring system to diagnose and stage peripheral neuropathy.

Editor's Comment :

- There is a significant association between autonomic neuropathy and diabetic peripheral neuropathy. Severe peripheral neuropathy can be associated with autonomic neuropathy. Also, hypoglycemia and neuroglycopenia patients have a higher predilection to develop autonomic neuropathy. Hence, detecting peripheral neuropathy and having a low index of suspicion for autonomic neuropathy can go a long way in reducing morbidity and mortality of patients with autonomic neuropathy.

Diabetic Autonomic Neuropathy (DAN) is a well-studied type of neuropathy that occurs due to an imbalance between the adrenergic and cholinergic systems[5]. It can have multisystem implications such as cardiovascular (cardiac autonomic neuropathy), gastrointestinal (gastroparesis, constipation, diarrhea), sudomotor (anhidrosis, non-healing foot ulcer) and genitourinary (cystopathy, sexual dysfunction)[6].

A cross sectional study done by Low PA, *et al* in Rochester, Minnesota, using Autonomic Symptom

Department of General Medicine, Manipal Academy of Higher Education, Manipal, Karnataka 576104
[1]MBBS, MD, Assistant Professor
[2]MBBS, MD, Assistant Professor and Corresponding Author
[3]MBBS, MD, Professor
[4]MBBS, MD, Associate Professor, Department of Physiology
[5]MBBS, MS, Professor, Department of General Surgery
Received on : 07/01/2024
Accepted on : 19/02/2024

How to cite this article : Autonomic Neuropathy in Patients with Diabetic Peripheral Neuropathy: A Cross Sectional Study. Shridhar M, Kamath PA, Vidyasagar S, Pallavi L C, Kedage V. *J Indian Med Assoc* 2025; **123(3):** 28-34.

Profile (ASP) and Composite Autonomic Severity Score (CASS) showed the prevalence of DAN of 54% in Type 1 DM and 73% in Type 2 DM[7]. A study done in Maharashtra, India in 2017, estimated the widespread presence of autonomic affection upto 58% in patients with type 2 DM[8].

Cardiac Autonomic Neuropathy (CAN) is a grave complication of Diabetes Mellitus. CAN results from damage to the autonomic nerve fibers that innervate the heart and blood vessels which can affect heart rate and cause change in vascular dynamics[9]. CAN manifests as a spectrum, ranging from resting tachycardia and fixed Heart Rate to arrhythmias, severe orthostatic hypotension, and silent myocardial infarction[3]. Thus, it can lead to perilous sequelae.

A study done in western population showed that 50% of diabetic patients with diabetic polyneuropathy have asymptomatic CAN[7]. 100% of symptomatic CAN present classical peripheral neuropathy[10]. A study done by Shukla, *et al* in 2014 in Kanchipuram, Tamil Nadu, India using CAN function testing showed a prevalence of 53.2%[11]. In type 2 diabetes, the prevalence of CAN positively correlates with duration of diabetes and has been elaborated in up to 60% of patients with type 2 diabetes after 15 years[7]. In addition, CAN has been found detected in patients with pre-diabetes or metabolic syndrome[12].

Often, DAN can be asymptomatic yet lead to an adverse outcome. Unexpectedly high occurrence of sudden cardiorespiratory deaths during and after surgery in diabetics with evidence of DAN was observed in a study done by Care D, *et al*[13]. CAN is strongly associated with a 5-fold increased risk of cardiovascular mortality as per a metanalysis study done by Ziegler D[14]. Prevention of DAN will eliminate hypoglycemic unawareness and neuroglycopenia, especially in the elderly. Anticipating a high risk of DAN in patients with peripheral neuropathy is of great importance in reducing morbidity and mortality due to early screening and intervention. As far as we know studies to show relationship between DAN and peripheral neuropathy are very few.

This study was carried out to determine the prevalence of DAN in DPN and its clinical implications. As a secondary objective we tried to find a relation between DAN and patients with hypoglycemia who presented with neuroglycopenia.

Materials and Methods

A tertiary care hospital based cross-sectional study was conducted among patients attending OPD or admitted in ward in between August, 2019 to August, 2021 meeting the inclusion-exclusion criteria. Ethical clearance was obtained from the Institutional Ethics Committee (IEC) of KMC (Kasturba Medical College) & Hospital, Manipal (IEC 580/2019). The study has been registered with Clinical Trials Registry of India (CTRI/2019/10/021742). Written informed consent was taken.

Sample size was calculated using the formula that, to estimate proportion of AN in DPN at 30% prevalence with 95% confidence level and relative precision of 20%, 233 DPN needed to be enrolled for the study. Only a proportion of subjects, ie, those with positive bedside CAN testing or symptoms of AN were to be subjected to CAN function testing. This was a time bound study and due to COVID -19 related restrictions, 120 subjects were recruited. Patients aged 18 years and above were asked questions based on a standard proforma regarding co-morbidities pertaining to diabetic peripheral neuropathy, hypoglycemia symptoms and autonomic symptoms. A thorough physical examination was done including anthropometry, pulse rate and Blood Pressure supine and standing. Laboratory investigations to diagnose diabetes and to rule out other systemic illness were done. Patients with history of drugs likely to confound analysis like beta blockers, clonidine, steroids, phenytoin, cisplatin, vincristine, amiodarone, fluoroquinolones, isoniazid were not included. Those suffering from diseases like chronic kidney disease, chronic liver disease, Human Immunodeficiency Virus infection, vitamin B12 deficiency, patients with severe systemic disease and unstable patients were excluded from the study.

Subjects were tested for peripheral neuropathy, according to the ADA guidelines 2017[1]

Michigan Neuropathy Screening Instrument (MNSI)[15] was used for scoring for assessment of neuropathy. In the patient history part, a score of $\geq$7 was taken as positive for the DPN. In the examination part, $\geq$8/10 was considered to be positive for the presence of DPN. Permission was obtained to use the scoring system which is attached.

Nerve Conduction Study (NCS) was done, using standard instruments and the severity and type of neuropathy (axonal/demyelinating) was determined.

Those in whom peripheral neuropathy was detected were included in the study. These patients were further tested for evidence of autonomic neuropathy.

CAN Function tests were done (Bedside)[9] :

Resting Tachycardia : Heart Rate (HR) more than 100/min was taken as tachycardia

Orthostatic Hypotension : BP of the subject was taken while lying down quietly as well as when standing. The postural fall in BP after 3 min was recorded (Abnormal is a drop of >20mmHg systolic and/or >10mmHg diastolic BP after 3minutes of standing).

Further CAN function testing was done by Department of Physiology, KMC Manipal, in Patients with autonomic dysfunction symptoms, (or) Patients with abnormal bedside autonomic function testing (or) Patients with features of neuroglycopenia

Hypoglycaemic subjects were identified as per WHO definition[16], ie, those who presented with blood glucose <60mg/dL and symptoms of hypoglycaemia which resolved with glucose correction were included.

Neuroglycopenia patients were identified as hypoglycaemic patients who had additional symptoms[17] like abnormal mentation, anxiety, irritability, personality change, confusion, delirium, stupor, or coma. In our study, 30 patients had hypoglycaemia out of which 19 presented with neuroglycopenia.

CAN Function Tests done by Department of Physiology, KMC Manipal :

Deep Breathing HR Variability : The subjects were requested to sit quietly and breathe deeply (10 s/ breath) for a total of 1 min. ECG was recorded consistently throughout the period. Points where each inspiration and expiration started was marked. The maximum HR when in inspiration(I) and minimum HR throughout expiration (E) in each breathing cycle were measured and expressed as mean for the six measured cycles as beats/min. E/I ratio was calculated. (Normal response >15 beats/min, borderline 11-14 beats/min; abnormal response <10beats/min[18]

Immediate HR Response to Standing : Subject was asked to lie comfortably on the bed and HR was recorded on an ECG machine. Then he was asked to stand up unaided and at that point a marking was done on the ECG. After this, the shortest RR interval at or around the 15th beat and largest RR interval at or around the 30th beat after starting was measured with a ruler. The HR response was expressed as 30:15 ratio (normal if >1.04; borderline between 1.01 and 1.03; and abnormal if <1)[18]

Isometric Hand Grip Test : The subject was asked to grip an inflated BP cuff using the hand of the dominant arm for a few seconds, for three times. The highest of the three readings (maximum voluntary contraction) was recorded. Subsequently, they were instructed to simply maintain handgrip and results were noted as the difference between the highest Diastolic BP (DBP) during handgrip exercise and the mean of three DBP readings before onset of handgrip (normal response >16 mmHg; borderline 11-15 mmHg; abnormal <10mmHg)[18]

Valsalva Ratio : The subjects were instructed to lie supine and then blow into a mouthpiece connected to a mercury sphygmomanometer and hold it at a pressure of 40 mmHg for 15seconds while ECG was recorded. ECG taken after this maneuver in lead II and V1 was observed and the ratio of the longest RR interval to the shortest RR interval was calculated (Valsalva ratio). Normal Valsalva ratio is >1.21 and values <1.2 were considered abnormal[18]

CAN positive subjects were graded as:

Subclinical phase : Decreased HR variability

Early phase : Resting tachycardia

Advanced stage : Exercise intolerance, orthostatic hypotension, cardiomyopathy with left ventricular dysfunction, silent MI

Analysis was done using SPSS software version 16. Continuous variables were demonstrated as mean and Standard Deviation (SD) or median. Discrete variables were expressed as percentages. P values were calculated to determine statistical significance.

Results

Baseline Characteristics (Table 1) :

Clinical Profile of Hypoglycemia and Neuroglycopenia :

Among the 30 hypoglycemia patients, gender was distributed equally. 15 had resting tachycardia. 9 had postural hypotension. 23 subjects had features of autonomic neuropathy. 24 subjects had severe diabetic peripheral neuropathy.

Table 1 — *Characteristics of study population (n=120)*

Characteristic		Total (%)
Age (years)	31 - 40	5(4.2)
	41 - 50	20(16.7)
	51 - 60	40(33.3)
	61 - 70	31(25.8)
	Above 70	24(20.0)
Sex	Male	74(61.7)
	Female	46(38.3)
BMI (kg/m^2)	<18.5	5(4.2)
	18.5 - 22.9	16(13.3)
	23 - 24.9	28(23.3)
	≥25	71(59.2)
Resting Heart Rate (beats/min)	<100	57(47.5)
	>100	63(52.5)
Postural Hypotension	Absent	79(65.8)
	Present	41(34.2)
HbA1C (%)	<6.5	6(5.0)
	>6.5	114(95.0)
FBS (mg/dl)	<140	17(14.2)
	>140	103(85.8)
PPBS (mg/dl)	<200	21(17.5)
	>200	99(82.5)
Neuroglycopenia	Present	19(15.8)
	Absent	101(84.2)
Hypoglycemia	Yes	30(25.0)
	No	90(75.0)
Neuropathy Type	Amyotrophy	9(7.5)
	DSPN – mixed type	94(78.3)
	DSPN – motor	3(2.5)
	DSPN – sensory	12(10.0)
	Mononeuritis multiplex	1(0.8)
	Mononeuropathy	1(0.8)
Neuropathy Symptom Severity	Absent	6(5.0)
	Low	24(20.0)
	Moderate	55(45.8)
	High	35(29.2)
Neuropathy Sign Severity	Absent	22(18.3)
	Low	61(50.8)
	Moderate	33(27.5)
	High	4(3.3)
Neuropathy Severity - Overall	Mild/Moderate	28(23.3)
	Severe	92(76.7)
Duration Of Diabetes (years)	<10	18(15.0)
	10-20	34(28.3)
	>20	68(56.7)
Can Function Testing	Absent	50(41.7)
	Subclinical	7(5.8)
	Early	57(47.5)
	Late	6(5.0)
Autonomic Neuropathy	Present	47(39.2)
	Absent	73(60.8)

Among the 19 patients presenting with neuroglycopenia, 12 were males and 7 were females. 12 had resting tachycardia and 7 had postural hypotension. 17 had severe autonomic neuropathy. 15 had severe peripheral neuropathy.

Autonomic Neuropathy and Clinical Profile : Among 76 autonomic neuropathy patients, 49 were males and 27 were females. 50 patients were diabetic for longer than 10 years. 46 subjects had poor glycemic control. 17 patients had neuroglycopenia.

Diabetic Peripheral Neuropathy and Autonomic Neuropathy :

Among 76 patients with autonomic neuropathy, 65 had severe peripheral neuropathy, and it is statistically significant(p=0.003)

Among 76 patients with autonomic neuropathy, the most common type of peripheral neuropathy was found to be distal symmetric polyneuropathy (DSPN) (67 in number) in our study.

Discussion

Prevalence of Autonomic Neuropathy in Peripheral Neuropathy :

In our study, out of 120 diabetic peripheral neuropathy patients, 76 subjects had DAN. Hence prevalence of DAN in our study is 63.3%. In 14 subjects out of 19 neuroglycopenia subjects had DAN, prevalence being 73.7%.

Ahmed, *et al* in 2001 in Saudi Arabia found that out of 48 DAN patients, 32 had peripheral neuropathy[16]. It was a cross sectional study which enrolled 120 subjects. However, the study design was different from ours in that the baseline population was DAN patients who were further tested for diabetic peripheral neuropathy.

Sukla, *et al* did a case control study in 2016, which enrolled 126 subjects, where 62 subjects had DAN (53.2% prevalence). In this study, all subjects underwent objective assessment and hence had a lower prevalence[8]. Our study included subjective data like assessment of symptoms of autonomic neuropathy as well.

SEARCH trial done in 2006, in United States was a cohort study which included 1646 patients out of which 252 were type 2 diabetes mellitus. 43 subjects had DAN (17% prevalence)[17]. However, in this study only heart rate variability was measured. Other objective measurements were not done as done in our study. Also, this study included only adolescent age group. DAN has been found to increase with increasing age[18], hence our study had a higher prevalence.

Duration of Diabetes and Autonomic Neuropathy:

Our study had 68 subjects with duration of diabetes >20 years out of which 50 had DAN and the association was found to be significant (p=0.025), as summarised in Fig 2.

Seung-Hyun, *et al* did a cohort study in 2008 in South Korea which enrolled 1021 subjects. Odds ratio was found to be 1.15 for duration >15 years however it can be highlighted that duration of diabetes in their sample were equally dispersed[19]). Our study had most patients in the age group >20 years. Since our baseline population had peripheral neuropathy incidence of which is known to increase with age[20].

A cohort study done by Jaiswal, *et al* in 2006 in US included 252 subjects out of which 40 patients had duration of diabetes >10 years[21]. Only 5 had DAN and 35 did not have the same. This study showed a negative association however it could be slightly skewed as only adolescent age group was included, it is highly likely that older adults who would have peripheral neuropathy were missed.

DAN increases with duration of diabetes as various mechanisms[22] like metabolic damage of nerve fibers, neurovascular compromise, activation of the polyol pathway, increase in oxidative stress progressively increase with time.

Glycemic Control and Autonomic Neuropathy :

Most of DAN patients had poor glycemic control however the association was not significant as at baseline to start with most patients had poor glycemic control. In our study, 70 subjects had poor glycemic control, out of which 46 had DAN. 44 subjects had fair glycemic control out of which 27 had DAN. 6 subjects had good glycemic control out of which 3 had DAN. The p-value, however, was not significant probably because at baseline most subjects had poor glycemic control, as is highlighted in Fig 2.

In 2010 Hoeldtke et al examined 37 individuals with recent onset diabetes and followed them up for 3 years. They concluded that oxidative stress causes increased incidence of DAN, similar to our study[22]. Wessells et al included 761 men with diabetes and followed them from 1983 to 1989. It was found that of the study subjects, 23% reported erectile dysfunction, which is one of the features of DAN[23].

It is well known that hyperglycemia is a major driving force for most of the complications of diabetes. High levels of blood and cytoplasmic glucose causes upregulation of various metabolic pathways that can cause increased oxidative stress, which can cause chronic tissue damage. Diabetic peripheral neuropathy being one of the microvascular complications of diabetes has been known to be more in patients with poor glycemic control.

Type and Severity of Peripheral Neuropathy and Autonomic Neuropathy :

In our study 76 subjects had DAN. Also, out of this, 67 had DSPN type of neuropathy. The association of type of peripheral neuropathy and DAN did not come as significant due to small sample size and most subjects had DSPN type of peripheral neuropathy, as per Fig 3b.

It was observed that 90 had severe and 30 had mild to moderate severity of peripheral neuropathy. Among those with severe disease, most (65) had DAN whereas DAN was present in only 11 subjects with mild/moderate peripheral neuropathy. This association has come as statistically significant (p=0.003) and is shown in Fig 3a.

A cross sectional study done by Ahmed, *et al* in 2001 in Saudi Arabia included 120 subjects out of which 48 had cardiac neuropathy among which 32 had peripheral neuropathy[16]. However, the design of the study was such that initially the group of CAN was identified and among them testing for peripheral neuropathy was done.

There have been very few Indian studies which have tried to prove higher chance of developing DAN among peripheral neuropathy patients. As per detailed literature review, not many studies have been done that attempt to correlate type of peripheral neuropathy or severity of peripheral neuropathy with DAN.

Peripheral neuropathy and DAN can be postulated to be interrelated and predictable of each other due to common causative mechanisms.

Cardiac Autonomic Neuropathy :

In our study, 73 had CAN. 63 had only resting tachycardia and 41 had only postural hypotension. We had included bedside testing ie, detecting resting tachycardia and postural hypotension and specific testing in physiology lab. Most studies that evaluated cardiac neuropathy focussed on measurement of only heart rate variability[19].

Damage to the autonomic fibres that innervate the heart due to neuropathy causes imbalance between sympathetic and parasympathetic system and can present as CAN[24].

Hypoglycemia, Neuroglycopenia and Autonomic Neuropathy :

In our study, out of the 19 hypoglycemic subjects who presented with neuroglycopenia, 17 had DAN, and

this association was found to be significant, as highlighted in Fig 2, though our study may have overestimated DAN due to inclusion of resting tachycardia as one of the parameters.

A cross sectional study done by Hepburn, *et al* with 302 subjects in 1990 in London showed that out of 21 neuroglycopenia subjects, 14 had autonomic dysfunction[25].

DAN is a risk factor for developing neuro-glycopenia as it causes obliteration of standard epinephrine response to hypoglycemia[26]. The presence of DAN, however, further attenuates the epinephrine response to hypoglycemia in diabetic subjects after recent hypoglycemic exposure[27].

Until recently, diabetic peripheral neuropathy and DAN were considered as two separate entities and there are several studies that demonstrate risk factors in both in a separate manner. However, DAN can be potentially life threatening and may remain silent for several years leading to a grave outcome[18]. On the contrary, peripheral neuropathy is a thoroughly studied complication and routinely sought for while examining a patient of diabetes mellitus.

Hence it would be of real practical use if there was a relationship between peripheral neuropathy and DAN which would help in earlier diagnosis, identification of high-risk individuals, prevent neuroglycopenia, and hence overall can lead to a favourable outcome.

The value of CAN in diagnosing autonomic neuropathy cannot be overestimated[28]. Also, there are very few international and no Indian study which has tried to extrapolate peripheral neuropathy to DAN.

Conclusion

Prevalence of DAN is 63.3% among subjects with diabetic peripheral neuropathy. CAN was found in 58.3% among subjects with diabetic peripheral neuropathy. DAN was more common in males than in females. Duration of diabetes is a significant risk factor in the development of DAN. Distal symmetrical polyneuropathy sensory type has the maximum predilection to develop into DAN. More the severity of peripheral neuropathy, the more the chance of developing DAN. Hypoglycemic patients who present with neuroglycopenia have significantly higher predilection of having DAN.

Strengths of the Study :

The present study is among the few Indian studies that have studied autonomic neuropathy among diabetes mellitus patients with peripheral neuropathy. To the best of our knowledge, there have been very few Indian studies that have documented an association between autonomic neuropathy and type of diabetic peripheral neuropathy. There is also not much data available on the association of neuroglycopenia and autonomic neuropathy in our country.

Limitations of the Study :

The study was cross sectional in design, hence participants could not be followed up for progression or new development of autonomic neuropathy or its manifestations.

Conflict of Interest : None

Funding : No funding was obtained for this study.

References

1 Pop-busui R, Boulton AJM, Feldman EL, Bril V, Freeman R, Malik RA, *et al* — Diabetic Neuropathy/ : A Position Statement by the Diabetic Neuropathy. 2017; **40(1):** 136-54.
2 Verrotti A, Prezioso G, Scattoni R, Chiarelli F — Autonomic neuropathy in diabetes mellitus. *Front Endocrinol (Lausanne)* 2014; **5:** 205.
3 Vinik AI, Erbas T — Recognizing and treating diabetic autonomic neuropathy. *Cleve Clin J Med* 2001; **68(11):** 928-930,932,934-944.
4 Low PA, Benrud-Larson LM, Sletten DM, Opfer-Gehrking TL, Weigand SD, O'Brien PC, *et al* — Autonomic symptoms and diabetic neuropathy: a population-based study. *Diabetes Care [Internet]* 2004; **27(12):** 2942-7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15562211
5 Birajdar SV, Chavan SS, Munde SA, Bende YP — A Study of autonomic nervous system dysfunction among patient with diabetes mellitus/ : a cross sectional study. *Int J Adv Med* 2017; **4(2):** 406-11.
6 Agashe S, Petak S — Cardiac Autonomic Neuropathy in Diabetes Mellitus. *Methodist Debakey Cardiovasc J* 2018; **14(4):** 251-6.
7 Low PA, Vernino S, Suarez G — Autonomic dysfunction in peripheral nerve disease. *Muscle Nerve* 2003; **27(6):** 646-61.
8 Sukla P, Shrivastava SR, Shrivastava PS, Rao NL — Assessment of the cardiac autonomic neuropathy among the known diabetics and age-matched controls using noninvasive cardiovascular reflex tests in a South-Indian population: A case-control study. *Avicenna J Med* 2016; **6(3):** 81-5.
9 Ziegler D, Voss A, Rathmann W, Strom A, Perz S, Roden M, *et al* — Increased prevalence of cardiac autonomic dysfunc-

tion at different degrees of glucose intolerance in the general population: the KORA S4 survey. *Diabetologia* 2015; **58(5):** 1118-28.

10 Martin CL, Albers JW P-BRDRG — Prevalence of diabetic peripheral neuropathy and its relation to glycaemic control and potential risk factors/ : the EURODIAB IDDM Complications Study. *Diabetologia* 1996; **39:** 1377-84.

11 Ziegler D — Diabetic cardiovascular autonomic neuropathy: Clinical manifestations and measurement. *Diabetes Rev* 1999; **7:** 342-54.

12 Herman WH, Pop-Busui R, Braffett BH, Martin CL, Cleary PA, Albers JW, *et al* — Use of the Michigan Neuropathy Screening Instrument as a measure of distal symmetrical peripheral neuropathy in Type 1 diabetes: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications. *Diabet Med* 2012; **29(7):** 937-44.

13 Care D, Suppl SS — Introduction/ : Standards of Medical Care in Diabetes 2019; **42(January):** 2018-9.

14 Hypoglycemia ADAW on. Defining and Reporting Hypoglycemia in Diabetes: A report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care [Internet]* 2005; **28(5):** 1245-9. Available from: https://doi.org/10.2337/diacare.28.5.1245

15 Dimitropoulos G, Tahrani AA, Stevens MJ — Cardiac autonomic neuropathy in patients with diabetes mellitus. *World J Diabetes* 2014; **5(1):** 17-39.

16 Ahmed AM, Hussein A, Ahmed NH — Diabetic autonomic neuropathy. *Saudi Med J* 2000; **21(11):** 1034-7.

17 Jaiswal M, Divers J, Urbina EM, Dabelea D, Bell RA, Pettitt DJ, *et al* — Cardiovascular autonomic neuropathy in adolescents and young adults with type 1 and type 2 diabetes: The SEARCH for Diabetes in Youth Cohort Study. *Pediatr Diabetes [Internet]* 2018; **19(4):** 680-9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29292558

18 Balcýoðlu AS, Müderrisoðlu H — Diabetes and cardiac autonomic neuropathy: Clinical manifestations, cardiovascular consequences, diagnosis and treatment. *World J Diabetes* 2015; **6(1):** 80-91.

19 Ko S-H, Park S-A, Cho J-H, Song K-H, Yoon K-H, Cha B-Y, *et al* — Progression of cardiovascular autonomic dysfunction in patients with type 2 diabetes: a 7-year follow-up study. *Diabetes Care* 2008; **31(9):** 1832-6.

20 D'Souza M, Kulkarni V, Bhaskaran U, Ahmed H, Naimish H, Prakash A, *et al* — Diabetic Peripheral Neuropathy and its Determinants among Patients Attending a Tertiary Health Care Centre in Mangalore, India. *J Public health Res* 2015; **4(2):** 450.

21 Ang L, Jaiswal M, Martin C P-BR — Glucose control and diabetic neuropathy: lessons from recent large clinical trials. *Curr Diab Rep* 2016; **14(9):** 528.

22 Hoeldtke RD, Bryner KD, McNeill DR, Hobbs GR, Riggs JE, Warehime SS, *et al* — Nitrosative stress, uric Acid, and peripheral nerve function in early type 1 diabetes. *Diabetes* 2002; **51(9):** 2817-25.

23 Wessells H, Penson DF, Cleary P, Rutledge BN, Lachin JM, McVary KT, *et al* — Effect of intensive glycemic therapy on erectile function in men with type 1 diabetes. *J Urol* 2011; **185(5):** 1828-34.

24 Sucharita S, Bantwal G, Idiculla J, Ayyar V, Vaz M — Autonomic nervous system function in type 2 diabetes using conventional clinical autonomic tests , heart rate and blood pressure variability measures. *Indian J Endocr Metab* 2011; **15(3):** 198-203.

25 Hepburn DA, Patrick AW, Eadington DW, Ewing DJ, Frier BM — Unawareness of hypoglycaemia in insulin-treated diabetic patients: prevalence and relationship to autonomic neuropathy. *Diabet Med* 1990; **7(8):** 711-7.

26 Freeman R, Baron R, Bouhassira D, Cabrera J, Emir B — Sensory profiles of patients with neuropathic pain based on the neuropathic pain symptoms and signs. *Pain [Internet]* 2014; **155(2):** 367-76. Available from: http://dx.doi.org/10.1016/j.pain.2013.10.023

27 Cryer PE — Hypoglycemia-associated autonomic failure in diabetes. *Am J Physiol Endocrinol Metab* 2001; **281(6):** E1115-21.

28 Duque A, Mediano MFF, De Lorenzo A, Rodrigues LFJ — Cardiovascular autonomic neuropathy in diabetes: Pathophysiology, clinical assessment and implications. *World J Diabetes* 2021; **12(6):** 855-67.