MAGNITUDE OF AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS PATIENTS OF MORE THAN 5 YEARS DURATION IN A TERTIARY CARE HOSPITAL OF ODISHA

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ABSTRACT

BACKGROUND

Autonomic neuropathy in type 2 diabetes mellitus patient is a serious and common complication of diabetes that is most often ignored by most of the clinicians. Diabetic autonomic neuropathy is among the least recognized and least understood complication of diabetes, despite its significant negative impact on survival and quality of life. It can involve multiple systems including cardiovascular, gastrointestinal, genitourinary, sudomotor, metabolic systems, and papillary dysfunctions.

MATERIALS AND METHODS

88 patients of type 2 diabetes mellitus of more than 5 years duration with the age more than 30 years of either sex were studied which as a descriptive study conducted in the department of general medicine of SCB medical college. Cardiovascular autonomic neuropathy was evaluated with regard to 5 parameters (heart rate, orthostatic hypotension, hand gripping test, QTc interval in ECG, exercise intolerance by treadmill test). For gastrointestinal autonomic neuropathy, genitourinary autonomic neuropathy, hypoglycaemic unawareness, pupillary abnormality, sweating disturbances, only signs and symptoms will be noted as most part of the evaluation would be done only in research laboratory, which requires specialized equipment. For erectile dysfunction, patients will be asked to fill questionnaires according to IIEF-5. (31,32). Prevalence of autonomic neuropathy was categorised into mild, moderate and severe among different age group of people, in both sexes based on duration of diabetes, body mass index (BMI) and was expressed as percentages.

RESULTS

Out of total 88 cases, 15 patients (17.0%) didn't have autonomic neuropathy, 22 patients (24.0%) had mild autonomic neuropathy, 33 patients (37.5%) had moderate autonomic neuropathy, 18 patients (20.3%) had severe autonomic neuropathy. Duration of diabetes and body mass index were risk factor whereas age and sex were not a risk factor for autonomic neuropathy in diabetes mellitus patients.

CONCLUSION

Overall prevalence of diabetic autonomic neuropathy in our study is 81.8%, among them mild is 24%, moderate is 37.5%, and severe is 20.3%. So, it should be evaluated in every diabetes patient of more than 5 years duration. Duration of diabetes and BMI are risk factors for autonomic neuropathy in diabetes mellitus patients.

KEY WORDS

Diabetes Mellitus, Diabetic Autonomic Neuropathy, Cardiovascular Autonomic Neuropathy

HOW TO CITE THIS ARTICLE: Meher M, Panda JK, Dash S, et al. Magnitude of autonomic neuropathy in type 2 diabetes mellitus patients of more than 5 years duration in a tertiary care hospital of Odisha. J. Evolution Med. Dent. Sci. 2019;8(12):863-867, DOI: 10.14260/jemds/2019/192

BACKGROUND

Diabetes mellitus (DM) is a heterogeneous chronic metabolic disorder principally characterised by persistent hyperglycaemia resulting from defects in insulin secretion, decreased glucose utilization, and increased glucose production. It also involves abnormality in carbohydrate, fat and protein metabolism.^(1,2,3)

Diabetes mellitus is classified on the basis of the pathogenic process that leads to hyperglycaemia.^(1,2)

1. Type 1 DM.
2. Type 2 DM.
3. Other specific types of DM.
4. Gestational DM.

The chronic hyperglycaemia of diabetes is associated with long term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart and blood vessels. Most of the mortality in diabetic population is due to its complication.⁽²⁾

Diabetic autonomic neuropathy (DAN) is a serious and common complication of diabetes that is most often ignored by most of the clinicians.⁽²⁾

Diabetic autonomic neuropathy (DAN) is among the least recognized and understood complication of diabetes despite its significant negative impact on survival and quality of life in people with diabetes.⁽⁴⁾ DAN goes completely unrecognised

'Financial or Other Competing Interest': None.
 Submission 23-02-2019, Peer Review 14-03-2019,
 Acceptance 18-03-2019, Published 25-03-2019.
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 DOI: 10.14260/jemds/2019/192

by patient and physician because of its insidious onset and protean multiple organ involvement. DAN can involve multiple systems including cardiovascular, gastrointestinal, genito-urinary, sudomotor, metabolic systems, pupillary dysfunction.^(4,5)

Cardiac autonomic neuropathy (CAN) is the most studied and clinically important form of DAN because of its life-threatening consequences and the availability of direct non-invasive tests of cardiovascular autonomic functions. CAN results from damage to the autonomic nerve fibers that innervate the heart and blood vessels and results in abnormalities in heart rate control and vascular dynamics.

The present study has been undertaken to determine the prevalence of autonomic neuropathy in diabetes mellitus patients of more than 5 years duration and correlation of autonomic neuropathy with references to age, sex, and duration of diabetes. This study will throw light on the importance of assessment of autonomic neuropathy during the course of type 2 diabetes mellitus, so that necessary therapeutic measures may be initiated early to decrease the morbidity and mortality associated with autonomic neuropathy.

Aims and Objective

- Magnitude of autonomic neuropathy in type 2 diabetes mellitus patient of more than five-year duration
- Correlation of diabetic autonomic neuropathy with age, sex, body mass index and duration of diabetes.

MATERIALS AND METHODS

Study Design

Cross Sectional Study.

Sampling Technique

Convenient sampling.

The present study is a tertiary care hospital based cross sectional study.

This study includes type 2 diabetes mellitus patients who attain OPD or

Emergency or admit in IPD at SCBMCH, Cuttack, Odisha.

All the patients from either sex who meet the following inclusion criteria are considered for inclusion in this study.

Sample size was taken based on the convenience of the study.

Inclusion Criteria

1. Age above 30 years.
2. Duration of type 2 diabetes mellitus -5 years or more.

All the patients from either sex who meet the following exclusion criteria are excluded from the study.

Exclusion Criteria

1. Patients with hypotension, congestive cardiac failure, ischaemic heart disease, hyperthyroidism, chronic renal failure, multiple system atrophy, Addison's disease.
2. Patients on medications such as vasodilators, diuretics, antiarrhythmic, beta blockers, alpha-agonist or alpha blocker.
3. Patient presented as fever due to any cause.

An informed consent for inclusion in this study will be obtained from all the patients. Each patient will undergo detailed history, through clinical examination, and biochemical tests as required. History regarding patient biodata, present illness, past illness, personal history, family history will be noted. Clinical examination including general examination and systemic examination will be performed.

All patients will be explained about the different manoeuvres like standing, hand grip and squeeze of ball. All recruited patients will be tested for-

1. Heart Rate- A resting heart rate of more than 100 beats per minute considered abnormal
2. Orthostatic Hypotension- Blood pressure will be first measured in right arm supine position by using the sphygmomanometer and then instruct the patient to stand up. Again, blood pressure will be measured as the same way. A fall in systolic blood pressure > 20 mm Hg and/or in diastolic blood pressure >10 mm of Hg will be considered abnormal.
3. Hand Gripping Test- blood pressure of the patient will be first measured in supine position. Instruct to the patient to squeeze a small ball in his/her hand for about 5 min while lying in bed and again blood pressure will be measured by using sphygmomanometer. An increase in diastolic blood pressure < 15 mm hg is abnormal.
4. ECG Recording-QTc interval $\geq$ 440 ms will be considered as abnormal.
5. Exercise Intolerance - all patients undergo treadmill test to know the reduced response in heart rate and blood pressure during exercise. Those patients whose heart rate is not achieved target heart rate during exercise considered as abnormal and whose blood pressure is not achieved target during exercise considered as abnormal.

No Autonomic Neuropathy

All five tests normal

Mild Autonomic Neuropathy

One of the three heart rate tests abnormal

Moderate Autonomic Neuropathy

Two or more of the heart rate tests Abnormal or one of the blood pressure tests normal.

Severe Involvement

Two or more of the heart rate tests abnormal plus one of the blood pressure tests is normal or both blood pressure tests abnormal.

For gastrointestinal autonomic neuropathy, genitourinary autonomic neuropathy, hypoglycaemic unawareness, pupillary abnormality, sweating disturbances, only sign and symptoms will be noted as most part of the evaluation done only in research laboratory, requires specialized equipment. For erectile dysfunction patient will be asked questionnaire according to IIEF-5.⁽⁶⁾

Statistical Analysis

A master chart was prepared by collecting all the information in Microsoft office excel sheet. Then data are analysed by using SPSS software. P value was calculated by chi-square analysis and independent "t test".

Evaluation of Autonomic Neuropathy

- A) Cardiovascular autonomic neuropathy
1. Resting tachycardia.
 2. Orthostatic hypotension.
 3. Abnormal Hand gripping test.
 4. Qtc interval > 440 msec.
 5. Exercise intolerance (by TMT).
- B) Gastrointestinal autonomic neuropathy
1. Gastroparesis.
 2. Constipation.
 3. Diarrhoea.
 4. Nocturnal diarrhoea alternating with constipation.
 5. Faecal incontinence.
- C) Genitourinary autonomic neuropathy
1. Sign and symptoms of neurogenic bladder.
 2. Erectile dysfunction in male.
 3. Retrograde ejaculation in male.
 4. Sexual dysfunction in female.
- D) Sudomotor
1. Anhidrosis.
 2. Gustatory sweating.
 3. Heat intolerance.
 4. Dry skin.
- E) Hypoglycaemic unawareness
- F) Pupillary dysfunction
1. Impaired adaptation to ambient light.
 2. Argyll Robertson pupil.

RESULTS

Gender	Number	Percentage	Mean Age (Years)
Male	59	67%	57.5 ± 7.28
Female	29	33%	53.4 ± 8.45
Total	88	100%	

Table 1. Gender Distribution of Study Population

Out of 88 cases of type 2 diabetes mellitus 59 (67%) were male and 29(33%) are female. Mean age of male population is 57.5 ± 7.28 and for female is 53.4 ± 8.45.

Age Groups (Yrs.)	Male	Female	Total
31 - 40	1 (1.1%)	2 (2.2%)	3 (3.04%)
41 -50	19 (21.5%)	6 (6.8%)	25 (28.4%)
51 - 60	25 (28.4%)	13 (14.7%)	38 (43.1%)
61 - 70	12 (13.6%)	7 (7.9%)	19 (21.5%)
71 - 80	2 (2.2%)	1 (1.1%)	3 (3.04%)

Table 2. Age Wise Distribution Among Cases

Highest no. of patients was in the age group of 51-60 yrs. 38 patients (43.1%) were in this group, among them 25 (28.4%) were male and 13(14.7%) were female.

Lowest no. of patients was in the extreme age group i.e., 31- 40 yrs., and 71-80 yrs. Both groups had 3 patients (3.04%).

Out of 59 male diabetic cases, 9 (10.2%) had no autonomic neuropathy, 15 (17.0%) had mild autonomic neuropathy, 22 (25%) had moderate autonomic neuropathy, 13 (14%) had severe autonomic neuropathy.

Out of 29 female diabetic cases, 6 (6.8%) had no autonomic neuropathy, 7 (7.9%) had mild autonomic

neuropathy, 11 (12.5%) had moderate autonomic neuropathy, 5 (5.6%) had severe autonomic neuropathy.

Sex	Diabetic Autonomic Neuropathy				Total
	Absent	Mild	Moderate	Severe	
Male	9 (10.2%)	15 (17.0%)	22 (25%)	13 (14.7%)	59 (66%)
Female	6 (6.8%)	7 (7.9%)	11 (12.5%)	5 (5.6%)	29 (33%)

Table 1. Prevalence of Autonomic Neuropathy in Both Sexes

Sex	DAN		p-Value
	Absent	Present	
Male	9	50	0.524
Female	6	23	

Table 2. Correlation of Autonomic Neuropathy with References to Sex

By chi-square analysis, the p value is 0.524. The result is not significant at p <0.05. So, we found sex is not a risk factor for autonomic neuropathy in diabetes mellitus patient.

Age (Years)	Diabetic Autonomic Neuropathy				Total
	Absent	Mild	Moderate	Severe	
31-40	0	2(2.2%)	0	1(1.1%)	3(3.4%)
41-50	6 (6.8%)	5 (5.6%)	7 (7.9%)	7 (7.9%)	25 (28.4%)
51-60	6 (6.8%)	9 (10.2%)	15 (17%)	8 (9.0%)	38 (43.1%)
61-70	3 (3.4%)	2 (2.2%)	12 (13.6%)	2 (2.2%)	19 (21.5%)
71-80	0	1(1.1%)	2(2.2%)	0	3(3.4%)

Table 3. Prevalence of Autonomic Neuropathy in Different Age Groups

In the age group 31-40, 1 patient had severe and 2 patients had mild autonomic neuropathy. In the age group of 41-50, 6 patients had no autonomic neuropathy, 5 patients had mild autonomic neuropathy, 7 patients had moderate autonomic neuropathy, 7 patients had severe autonomic neuropathy. In the age group of 51-60, 6 patients had no autonomic neuropathy, 9 patients had mild autonomic neuropathy, 15 patients had moderate autonomic neuropathy, 8 patients had severe autonomic neuropathy. In the age group of 61-70, 3 patients had no autonomic neuropathy, 2 patients had mild autonomic neuropathy, 12 patients had moderate autonomic neuropathy, 2 patients had severe autonomic neuropathy. In the age group of 71-80, 1 patient had mild autonomic neuropathy, 2 patients had moderate autonomic neuropathy.

	DAN		p-Value
	Absent	Present	
Age in Years Mean ±SD	54.53 ± 7.5	55.63 ± 8.4	0.643

Table 4. Correlation of Autonomic Neuropathy with Reference to Age

By using independent t test the p value is calculated as 0.643 which is not significant at p <0.05. By using binary

logistic regression, so we found that age is not a risk factor for development of autonomic neuropathy in diabetes mellitus patient.

Duration of Diabetes (Years)	Diabetic Autonomic Neuropathy				Total
	Absent	Mild	Moderate	Severe	
5 - 8	16 (18.0%)	5 (5.6%)	6 (6.8%)	11 (12.5%)	38 (40.9%)
8.1 - 12	9 (10.2%)	12 (13.6%)	16 (18.0%)	11 (12.5%)	47 (53.4%)
>= 12.1	0	0	4 (4.5%)	1 (1.1%)	5 (5.6%)

Table 5. Prevalence of Autonomic Neuropathy with Reference to Duration of Diabetes

In the 5-8 years duration of diabetes group, 16 patients had no autonomic neuropathy, 5 patients had mild autonomic neuropathy, 6 patients had moderate autonomic neuropathy, 11 patients had severe autonomic neuropathy. In the 8.1-12 years duration of diabetes group, 9 patients had no autonomic neuropathy, 12 patients had mild autonomic neuropathy, 16 patients had moderate autonomic neuropathy, 11 patients had severe autonomic neuropathy. In the >=12.1 years duration of diabetes group, 4 patients had moderate autonomic neuropathy, 1 patient had severe autonomic neuropathy.

	DAN		p-Value
	Absent	Present	
Duration of Diabetes in Years Mean $\pm$ SD	6.20 $\pm$ 1.78	8.36 $\pm$ 2.55	0.003

Table 6. Correlation of Autonomic Neuropathy with Reference to The Duration of Diabetes

The p value is calculated as 0.003 which is significant at $p < 0.05$. So, duration of diabetes is a risk factor for development of autonomic neuropathy in type 2 diabetes mellitus patient. With increase in duration of diabetes, chances of development of autonomic neuropathy increase.

BMI (Kg/m ²)	Diabetic Autonomic Neuropathy				Total
	Absent	Mild	Moderate	Severe	
<= 24.9	2 (2.2%)	2 (2.2%)	2 (2.2%)	1 (1.1%)	7 (7.9%)
25 - 29.9	11 (12.5%)	15 (17%)	16 (18.0%)	8 (9.0%)	50 (56.8%)
30 - 34.9	2 (2.2%)	5 (5.6%)	14 (15.8%)	8 (9.0%)	29 (33%)
35 - 39.9	0	0	1 (1.1%)	1 (1.1%)	2 (2.2%)
>= 40	0	0	0	0	0

Table 7. Prevalence of Autonomic Neuropathy with References to BMI

In BMI group of <= 24.9 kg/m², 2 patients had no autonomic neuropathy, 2 patients had mild autonomic neuropathy, 2 patients had moderate autonomic neuropathy, 1 patient had severe autonomic neuropathy. In BMI group of <=25-29.9 Kg/m², 11 patients had no autonomic neuropathy, 15 patients had mild autonomic neuropathy, 16 patients had moderate autonomic neuropathy, 8 patient had severe autonomic neuropathy. In BMI group of 30-34.9 kg/m², 2

patients had no autonomic neuropathy, 5 patients had mild autonomic neuropathy, 14 patients had moderate autonomic neuropathy, 8 patient had severe autonomic neuropathy. In BMI group of 35-39.9 kg/m², 1 patient had moderate autonomic neuropathy, 1 patient had severe autonomic neuropathy.

	DAN		p-Value
	Absent	Present	
BMI in KG/M2 Mean $\pm$ SD	27.34 $\pm$ 2.32	29.15 $\pm$ 2.79	0.0005

Table 8. Correlation of Autonomic Neuropathy with References to BMI

BY using independent t test, p value is calculated as 0.0005 which is significant at $p < 0.05$. We found that BMI is a risk factor for development of autonomic neuropathy. With increase in BMI, chances of development of autonomic neuropathy increases.

Autonomic Neuropathy	Male	Female	Total
Absent	9 (10.4%)	6 (7.8%)	15 (18.2%)
Mild	15 (17.04%)	7 (7.9%)	22 (24.0%)
Moderate	22 (25%)	11 (12.5%)	33 (37.5%)
Severe	13 (14.7%)	5 (5.6%)	18 (20.3%)

Table A. Overall Prevalence of Categories of Autonomic Neuropathy Among Cases

Out of total 88 cases, 15 patients (17.0%) didn't have autonomic neuropathy, 22 patients (24.0%) had mild autonomic neuropathy, 33 patients (37.5%) had moderate autonomic neuropathy, 18 patients (20.3%) had severe autonomic neuropathy.

So, the prevalence of autonomic neuropathy in our study is 81.8%. Among them mild is 24%, moderate is 37.5%, and severe is 20.3%.

DISCUSSION

In our study we found that the prevalence of autonomic neuropathy (TABLE-A) of diabetes patients of more than 5 years duration is 81.8%. Among them among them mild is 24%, moderate is 37.5%, and severe is 20.3%. In a study of S Aggarwal, et al found that the prevalence of DAN in the cohort studied was 70%. Amongst these, 22.9% had severe autonomic dysfunction with prevalence of definite and early neuropathy being 40% and 37% respectively.⁽⁷⁾ Studies by Ewing et al⁽⁸⁾ had found its prevalence as 63.93% with 39 out of 61 diabetics' examined testing positive for DAN whereas Valensi P. et al⁽⁹⁾ in his French multicentre study in the year 2003 reported its prevalence as 51%. Nijhawan et al⁽¹⁰⁾ documented its prevalence in 60% diabetics in India. The reported prevalence of DAN varies widely depending on the cohort studied and methods of assessment.

By chi-square analysis of Table -2. The p value is 0.524. The result is not significant at $p < 0.05$. By using binary regression analysis so we found sex is not a risk factor for autonomic neuropathy in diabetes mellitus patient and there is no correlation of autonomic neuropathy with respect to sex of the diabetic patient. In a study of S Aggarwal, et al no correlation of DAN could be assessed with respect to sex of the patients. Valensi P, et al in his study they could not find any correlation of DAN with respect to sex of the diabetic

patients.⁽⁹⁾ By using independent t test of Table-4. The p value is 0.643. The result is not significant at $p < 0.05$. By using binary logistic regression, so we found that age is not a risk factor for development of autonomic neuropathy in diabetes mellitus patient and there is no correlation of autonomic neuropathy with respect to age of the diabetic patient. In a study of S Aggarwal, et al no correlation of DAN could be assessed with respect to age of the patients. Valensi P, et al in his study they could not find any correlation of DAN with respect to age of the diabetic patients.

Development and degree of DAN is not an all or none phenomenon but a continuation of the progression of a disease process, its incidence increasing in direct proportion to the duration of the disease.⁽¹¹⁾ Table 6 shows, The p value is 0.003 (By using independent t test). the result is significant at $p < 0.05$. So we found that duration of diabetes is a risk factor for the development of autonomic neuropathy. With increase in duration of diabetes there is increase in proportion of moderate and severe autonomic neuropathy. Only moderate and severe autonomic neuropathy found in patients those had ≥ 12 -year duration of diabetes only moderate and severe autonomic neuropathy. Valensi P. et al⁽⁹⁾ and Kempler et al⁽¹²⁾ showed a significant correlation between prevalence of CAN and duration of diabetes ($p = 0.026$ and $p < 0.0001$ respectively). P Feifer⁽¹³⁾ even concluded that after a mean duration of 25 years of diabetes almost all diabetics will have autonomic dysfunction. A higher prevalence rate of CAN (70%) was observed with an early age of onset having mean duration of diabetes 2.67 ± 1.67 yrs. This further rose with increasing duration and all the cases with mean duration 14.25 ± 2.5 yrs. had autonomic dysfunction. Studies of S. Aggarwal et al, also found a linear relationship between the duration of disease and severity of dysautonomia. But in the present work, there was an increase in the severity of autonomic dis-function, 56.6% in 5-8 yrs duration of diabetes group to 82.9% in 9-12 yrs., duration group, to 100% in > 12 yrs., duration group.

Table-8 shows, the p value is 0.0005 (By using independent t test). The result is significant at $p < 0.05$. So, we found that BMI is a risk factor for the development of autonomic neuropathy. With increase in BMI of diabetic patient chances of development of autonomic neuropathy increases. There is no such study in which BMI is correlated with autonomic neuropathy in diabetes patient.

CONCLUSION

Diabetic autonomic neuropathy (DAN) is a common complication of type 2 diabetes mellitus. In our study, we found that the prevalence of DAN is 81.8%. So, DAN should be evaluated in all type 2 DM patients of > 5 -year duration as most often ignored by most of the clinicians. DAN goes completely unrecognised by patients and physicians because of its insidious onset and protean multiple organ involvement. In our study, we found that high prevalence of autonomic neuropathy associated with increase in duration of diabetes and BMI. However, the present study involves a

small number i.e. 88 cases; thus further studies involving larger number of cases is likely to throw better insight into the prevalence of diabetic autonomic neuropathy and its correlation over glycaemic control.

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