International Journal of Biomedical Research

ISSN: 0976-9633 (Online)
Journal DOI:10.7439/ijbr
CODEN:IJBRFA

Research Article

Frequency of Autonomic Neuropathy Occurrence among Diabetic Patients

Adnan Bashir Bhatti[*1], Farhan Ali[2], Siddique Akbar Satti[3] and Syed Irfan Ahmed[4]

[1]*Department of Medicine, Capital Development Authority Hospital, Islamabad, Pakistan*
[2]*Senior Registrar, Department of Medicine, Capital Development Authority Hospital, Islamabad, Pakistan*
[3]*Consultant Physician & Head of Department of Medicine, Capital Development Authority Hospital, Islamabad, Pakistan.*
[4]*Professor of Medicine, Department of Medicine, Benazir Bhutto Hospital, Rawalpindi, Pakistan*

***Correspondence Info:**

Dr. Adnan Bashir Bhatti, M.D.
Department of Medicine,
Capital Development Authority Hospital,
Islamabad , Pakistan
E-mail: dr.adnanbashir@gmail.com

Abstract

Objectives: Diabetic autonomic neuropathy (DAN) is the most common and grave complication of diabetes mellitus (DM). In this study, we determined the frequency of autonomic neuropathy among both type1 and type 2 diabetic patients in Pakistan.

Materials and Methods: This study was conducted at Capital Development Authority (CDA) Hospital, Pakistan. The adult patients who had DM for at least last five years were assessed for this study. Four cardiovascular reflex tests were performed on each patient. Pre-prandial and two hours postprandial blood glucose were also measured.

Results: A total of 200 patients were recruited for the study. Of them, 133 (66.5%) patients had autonomic neuropathy. Cardiovascular involvement was seen in 86 (43%), gastrointestinal involvement in 93(46%) and genitourinary involvement in 15 (7.5%) patients. The frequency of autonomic neuropathy did not differ between type 1 and type 2 DM patients (p=0.246). However, the frequency of autonomic neuropathy was found to be predominant among the subjects with long history of DM (p=0.016).

Conclusion: We conclude that frequency of autonomic dysfunction is more common among patients with long standing DM patients. Hence, all the diabetic patients with disease duration of more than 5 years should be evaluated for autonomic dysfunction.

Keywords: Diabetes mellitus, autonomic neuropathy, cardiovascular, gastrointestinal, genitourinary.

1. Introduction

Diabetes mellitus (DM) is a syndrome of disordered metabolism and inappropriate hyperglycemia due to either a deficiency of pancreatic secretion of insulin or to a combination of insulin resistance and an inadequate compensatory insulin secretion by the pancreas. DM patients are susceptible to long-term complications that cause morbidity and premature mortality. DM results when pancreatic beta cells are unable to maintain adequate insulin secretion to prevent hyperglycemia. A combination of genetic and environmental factors causes the underlying beta-cell failure[1].

In a survey by the World Health Organization (WHO), it was shown that in 1995, Pakistan was 8th among the top 10 countries with high prevalence of diabetes, with 4.3 million people diagnosed. However, it is estimated that in year 2025, Pakistan will be 4th on the list with 14.5 million people suffering from this disease[2]. As far as risk factors are concerned, WHO has reported that sedentary life style is one of the 10 leading causes of diabetes. In the national health survey of

Pakistan (1990–1994), it was observed that the prevalence of obesity and increased body mass index (BMI) were much higher in urban areas compared to the rural areas[3].

The global pandemic is highlighted mainly by type 2 DM and several factors have contributed to its predominance including: longevity, obesity, poor diet, sedentary life style and increasing urbanization. Diabetes mellitus is a group of metabolic disorders with the common manifestation of hyperglycemia. A chronic hyperglycemic state can result in damage to the heart, eyes, kidneys, nerves and blood vessels[1].

Diabetic neuropathy (DN) is a heterogeneous disorder that encompasses a wide range of abnormalities affecting sensory and motor nerves as well as the autonomic nervous system (ANS)[4]. It is the most common and grave complication of DM as symptoms may be confined to a single target organ or organ system.Diabetic autonomic neuropathy can result in silent heart attacks; kidney disease; gastrointestinal disturbances; inability to recognize hypoglycemia; and genitourinary abnormalities[4,5].

Despite its relationship to an increased risk of cardiovascular mortality and its association with multiple systems and impairments, the significance (mechanism of DAN, as well as Diabetic Neuropathy in general, is poorly understood) of DAN has not been fully appreciated. The reported prevalence of DAN varies widely depending on cohort studies and methods of assessment. DAN frequently coexists with peripheral neuropathies and other diabetic complications, but may be isolated[6,7]. Treatment of diabetic autonomic neuropathy can be difficult; it is therefore desirable to prevent this complication or once established, slow disease progression[8-10].

The purpose of this study is to measure the frequency of autonomic neuropathy among DM patients who have been suffering with this illness for at least last five years. Studies of various aspects of DM have been conducted in Pakistan and other countries, but limited data is still available regarding diabetic autonomic neuropathy.

2. Materials and Methods

2.1 Study subjects

The study subjects were recruited in Department of Medicine, Capital Development Authority Hospital, Islamabad, Pakistan between June 2008 and May 2009. Capital Development Authority Hospital is a tertiary care hospital. This was a prospective study and study subjects were recruited based on the convenience sampling method. The adult patients (>20 years) who had DM for at least last five years were recruited for this study. Patients with co-morbid history of myocardial infarction, malignancies, renal failure, liver cirrhosis, stroke, and those using vasodilator and sympatholytics agents were excluded from the study. This study protocol has been approved by ethical committee of Capital Development Authority Hospital and written consent was obtained from all the eligible patients.

2.2 Data collection and interpretation

All the patients were asked to fill up a questionnaire to collect their demographic and clinical information. Physical examination was carried out to assess their resting heart rate, beat to beat heart rate variation during deep breathing, postural hypotension, and heart rate response to the valsalva maneuver. Resting heart rate was monitoredusing and electrocardiogram. Postprandial and pre-prandial blood glucose levels were recorded. Heart rate of 100 beats per min or greater was taken as evidence of autonomic neuropathy.

2.3 Heart beat rate and hypotension assessment

Beat to beat heart rate variation was observed while the patient was asked to take a deep breathe. It was measured with the patient either in a sitting position or in a supine position. Briefly, the patient was asked to breathe deeply at 6 breaths a minute (breathing in for a count of 5 seconds and exhaling for a count of 5 seconds) for one minute. An ECG reading was recorded throughout the period of deep breathing and a marker was used to indicate the onset of each inspiration and expiration. The maximum and minimum RR intervals during each breathing cycle were measured and converted into beats per minute. The result was then expressed as the mean difference between maximum and minimum heart rates for the 6 measured cycles in beats/minute. A difference in heart rate of >15 beats/min was considered as normal and <10 beats/min was considered as abnormal. The ratio of R-R inspiration/R-R expiration was noted to be >1.

To assess the postural hypotension, systolic blood pressure was measured for each patient at supine and standing position. A fall of <10 mmHg was considered as normal response and fall of >20 mmHg with symptoms was considered abnormal and characterized as postural hypotension.

Next the heart rate response to the valsalva maneuver was assessed. The test was performed by the patient blowing into a mouth piece connected to a Sphygmomanometer as the patient was asked to blow at a pressure of 40 mm Hg for 15 seconds while a continuous ECG was recorded. The maneuver was performed 3 times with an interval of one minute in between. The result was expressed as the Valsalva ratio calculated as the ratio of the longest R-R interval after the maneuever to the shortest R-R interval during the maneuver. The mean of the three Valsalva ratios was then recorded (Normal Valsalva ratio>1, abnormal<1).

2.4 Blood glucose measurement

In order to measure the pre-prandial blood glucose levels, blood samples were obtained after over night fasting. To measure the postprandial glucose level, the blood samples were collected after 2 hours of their meal. After collecting the plasma by centrifugation, glucose level was measured using GOD-POD method.

2.5 Data Analysis

The statistical package for social sciences (SPSS, version 13.0) was used to enter and analyze the data. Chi-square t test and unpaired t test were used to compare the qualitative and quantitative data respectively.

3. Results

A total of 200 patients were recruited during the study period. The demographic and clinical details are given in **Table 1**. Among the 200 subjects, 93 were males and 107 were females. The mean age of the study population was 50.7 years (SD±9.2). The youngest was 21 years old and the oldest patient was 60 years of age. The majority of the patients were in the age range of 40 to 55 years.

Table 1: Demographic and clinical details of the study subjects

Category	Sub category	N (%) or Mean (SD)
Number of subjects	-	200
Gender, number (%)	Males Females	93 (46.5) 107 (53.5)
Age, mean in years (SD)	-	50.7 (9.2)
Type of diabetes, number (%)	Type 1 Type 2	23 (11.5) 177 (88.5)
Duration of diabetes, number (%)	5-10 years 10-15 years >15 years	46 (23) 81 (40.5) 73 (36.5)
Fasted glucose level, mg/dl (%)	<150	105 (52.5)
-	>150	95 (47.5)
Post-prandial glucose, mg/dl (%)	150-250	107 (53.5)
-	250-350	66 (33)
-	>350	27 (13.5)

The disease duration on average amongst the two hundred diabetic patients was 9.6 years (SD+3.8). The Minimum duration of illness was 5 years and the maximum duration of illness was 24 years. One hundred and seventy-seven (88.5%) patients had type 2 diabetes mellitus and twenty-three patients (11.5%) were afflicted with type 1 diabetes mellitus.

It was found that 95 patients (47.5%) had pre-prandial blood glucose level >150mg/dL, and 105 (52.5%) had <150 mg/dL. Post prandial blood glucose level was between 150-250mg/dL in 107 (53.5%) patients, 250-350 mg/dL in 66 (33%) patients and >350mg/dL in 27 (13.5%) patients.

A total of 133 (66.5%; 95% confidence interval: 59.43-72.57%) patients had autonomic neuropathy. Of these 133 patients, 18 (11.5%; 95% CI: 6.08-16.92%) had type 1 DM and 115 (88.5%; 95% CI: 83.08-93.92%) had type 2 DM. The frequency of autonomic neuropathy did not differ between type 1 and type 2 DM patients (p=0.246) (**Table 2**). However, the frequency of autonomic neuropathy was found to be predominant among the subjects with long history of DM (p=0.016). Other variables such as blood glucose level, gender difference and age did not affect the frequency of autonomic neuropathy occurrence.

Table 2: Characteristics of patients with autonomic neuropathy

Category	Diabetic patients		P value
	With AN (N =133)	Without AN (N=67)	
Age, years (SD)	52.5 (10.3)	49.8 (9.9)	0.856
Gender, number (%) Males/females	54/57	39/50	0.57
Type of diabetes Type 1/type 2	18/115	05/01/62	0.25
Fasted blood Glucose level, mg/dl (SD)	175 (25.2)	162 (21.4)	0.542
Postprandial blood glucose	295 (45.2)	262 (42.6)	0.742
Duration of diabetes	9.2 (2.3)	6.3 (1.2)	0.016

The gastrointestinal system was the most common system involved (**Table 3**). Ninety three (46.5%; 95% CI: 39.59-53.41%) out of 200 patients were afflicted with gastrointestinal symptoms, followed by manifestations of the cardiovascular system observed in 86 (43%; 95% CI: 36.14-49.86%) patients. The genitourinary system involvement was seen in 15 (7.5%; 95% CI: 3.85-11.15%) patients and gastrointestinal involvement was seen in 12 patients with type 1 diabetes mellitus and 81 with type 2 diabetes mellitus. Cardiovascular system involvement was seen in 74 patients with type 2 diabetes mellitus and 12 patients with type 1 diabetes mellitus. Genitourinary involvement was seen in 14 patients of type 2 DM and 1 patient with type 1 DM.

Table 3: Cumulative Autonomic neuropathy

Systemic involvement	Frequency (n= 200)			Percentage
	Type I	Type II	Total	
Gastrointestinal	12	81	93	46.5
Cardiovascular	12	74	86	43.0
Genitourinary	1	14	15	7.5

Early satiety was the most frequent gastrointestinal symptom among the affected group seen in 121 (60.5%; 95% CI: 53.73-67.27%) patients (**Table 4**). This was followed by epigastric discomfort, seen in 116 (58%; 95% CI: 51.16-64.84%) of patients. Nausea and vomiting was found in 87 (43.5%; 95% CI: 36.63-50.37%) patients whereas constipation and bloating occurred in about half of the affected group, i.e. in 56 (28%; 95%CI: 21.78-34.22%) patients. Nocturnal diarrhoea was least commonly seen, with only 31 (15.5%; 95% CI: 10.48-20.52%) patients affected.

Table 4: Symptoms associated with autonomic neuropathy

Type	Symptoms	Number of patients (%)
Gastrointestinal	Early satiety	121 (60.5)
	Nausea/vomiting	87 (43.5)
	Epigastric discomfort	116 (58)
	Bloating	56 (28)
	Nocturnal diarrhoea	31 (15.5)
	Constipation	56 (28)
Cardiovascular	Dizziness	58 (29)
	Resting tachycardia	52 (26)
	Sinus Arrhythmia	118 (59)
	Valsalva maneuver Abnormality	94 (47)
	Postural hypotension	32 (16)

Cardiovascular involvement was seen in 86 (43%) out of 200 patients. The results of clinical reflex testing showed sinus arrhythmia in 118 (59%; 95% CI: 52.18-65.82%) patients, abnormal response to valsalva maneuver was found in 94 (47%; 95% CI: 40.08-53.92%) patients. Dizziness was seen in more than half of total, i.e. in 58 (29%; 95% CI: 22.71-35.29%) patients. Resting tachycardia was seen in about 52 (26%; 95% CI: 19.92-32.08%) of the total patients with evidence of cardiovascular system autonomic neuropathy. Least frequently detected in the abnormal reflex test was postural hypotension found in 32 (16%; 95% CI: 10.92-21.08%) patients of study group (**Table 4**). Genitourinary system was the least frequently involved in this study group. Only 15 (7.5%; 95% CI: 3.85-11.15%) patients had evidence of urinary hesitancy, retention and impotence (erectile dysfunction).

4. Discussion

In this study, we found that 66% of DM patients were having autonomic neuropathy complications in a setting where the prevalence of DM is higher. Furthermore, we also found that the patients with long history of DM were found have higher risk for occurrence of autonomic neuropathy.

In this study, the majority of patients were with type 2 diabetes mellitus (88.5%) and there were only 11.5% patients with type 1 diabetes mellitus. However, there was no significant association between type of diabetes and occurrence of autonomic neuropathy. Poor glycemic control was common due to poor diabetic care, lack of education, noncompliance and poor dietary control. In our study, it was observed that the symptoms of autonomic neuropathy were negligible among the patients with adequate control of post prandial blood glucose and less duration of DM. However, patients with long duration of diabetes had higher frequency of diabetic autonomic neuropathy irrespective of blood glucose control. There is evidence that early intervention by tight glycemic control may influence the course of the disease, and early detection by simple autonomic reflex tests, even in long standing diabetes, can affect the disease progression[4,5,11-13]. Thus common treatment for all autonomic disorders should include alleviation of symptoms and tight glycemic control to prevent continued deterioration[12].

Estimates of the frequency of diabetic neuropathy dependent on the criteria used for diagnosis and specific population[13]. In one population based study of diabetic patients in Rochester, Minnesota, symptomatic visceral autonomic neuropathy had a prevalence of 5.5%. [4] The prevalence of symptoms of autonomic dysfunction and abnormal tests of autonomic nervous system function in diabetic clinic and tertiary referral centers are very high. Therefore, we could detect maximum number of autonomic neuropathy cases.

The cardiovascular system bears the brunt of autonomic neuropathy in DM. This may be responsible for certain disabling symptoms, painless myocardial infarction, and sudden deaths[4,5,14-17]. In our study, 43% of the patients showed the involvement of the cardiovascular system. In one study of 1171 diabetic patients in 22 diabetic centers in Germany, Austria and Switzerland, 25.3% with type 1 diabetes mellitus and 34.3% of patients with type 2 diabetes mellitus had evidence of cardiovascular autonomic neuropathy[4]. A Pakistani study showed 48% of the patients had type 1 DM and 76% patients with type 2 diabetes had cardiac autonomic dysfunction[18]. In another study with 33 patients, abnormal autonomic reflex was found in 72.3% patients. Abnormal valsalva was found in 15.2%, orthostatic hypotension in 9% and postural hypotension in 21.2% patients[16].

Most of our patients with two or more abnormal cardiovascular reflex tests had parasympathetic involvement. This shows progression of autonomic neuropathy is similar to other studies (from normal to parasympathetic and eventually sympathetic damage)[4,14,15]. In a study conducted by Chen et al., significant relationships were observed between cardiac autonomic neuropathy, duration of disease, control of blood glucose and other complications of diabetes[19].

In this study, gastrointestinal autonomic dysfunction was observed most frequently. In our study there is a high frequency of gastrointestinal symptoms especially early satiety, in more than half of the patients (60.5%) and epigastric discomfort in 118 (58%) patients, which indicates that significant association between glycemic control and disease duration. However, in a study of 33 diabetics, no patient was found with gastrointestinal involvement[16].

Genitourinary autonomic dysfunction was seen in only 7.5% patients in our study. Erectile dysfunction is commonly observed in such patients with researchers reporting figures varying from 35% to 75%.4 As shown in earlier study, impotence was very common affecting 9 (27%) out of 33 patients[16]. In another study, erectile dysfunction was found in 30% to 40% of diabetic men[21]. Erectile dysfunctions are very common but rarely reported symptoms of autonomic neuropathy due to the fact that patients feel embarrassed and are reluctant to discuss sexual complications openly.

5. Conclusions

Our study results altogether conclude that autonomic dysfunction is common in patients with long standing diabetes mellitus. Therefore, all the diabetic patients with disease duration of more than 5 years should be evaluated for autonomic dysfunction.

References

1. Brother KI. Diabetes treatment-bridging the divide". *N Engl J Med* 2007; 356: 149-501.
2. Iqbal F, Naz R. Patterns of diabetes mellitus in Pakistan: An over view of the problem. Pakistan J Med 2005; 44: 59-64.
3. Shera AS, Jawad F, Maqsood, A . Prevalence of Diabetes Mellitus in Pakistan. *Diabetes Res Clin Pract* 2007; 76: 219-222.
4. Vinik AL, Freeman R, Erbas T. Diabetic autonomic neuropathy. *Semin Neurol* 2003; 23: 365-372.
5. Vinik AL, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. *Diabetes Care* 2003; 26: 1553-1579.
6. Vinik AI, Erbas T. Recognizing and treating diabetic autonomic neuropathy. *Cleve Clin J Med* 2001; 68: 928-944.
7. Vinik AI. Diagnosing diabetic autonomic neuropathy. *Medscape Diabetes and Endocrinology* 2002; 4(2).
8. Casellini CM, Vinik AL. Clinical manifestation and current treatment options for diabetic neuropathies. *Endocr Pract* 2007; 13: 550-566.
9. Boulton AJ, Vinik AL, Avezzo JC, et al. Diabetic Neuropathies. *Diabetes Care* 2005; 18: 956-962.
10. Said G. Diabetic Neuropathy-A review. *Nat Clin Pract Neurol* 2007; 3: 331.
11. Stevens MJ. Diabetic Autonomic Neuropathy Updates literature review for version 19.1 January 2011. www. uptodate. Com.
12. The DCCT Research Group. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the diabetes control and complications Trial (DCCT). *Diabetologia* 1998; 41: 416-23.
13. Maser RE .Autonomic neuropathy: patient care. *Diabetes spectrum* 1998;11: 224-7.
14. Aydin KA, Gullulu S, Ozdemir B, Senturk T, Aydinlar A. The relationship between cardiac autonomic neuropathy and tei- index in patients with type-2 diabetes mellitus. *Acta Cardiol* 2008; 63: 629-33.
15. Schonauer M, Thomas A, Morbach S, Niebauer J, Schonauer U, Theile H. Cardiac autonomic diabetic neuropathy. *Diab Vasc Dis* 2008; 5: 336-44.
16. Noronha JL, Bhandarkar SD, Shenoy PN, Retnam VJ. Autonomic neuropathy in diabètes mellitus. *JPGM* 1981; 27: 1-6.
17. Witte DR, Tesfaye S, Chaturvedi N, et al. Risk factors for cardiac autonomic neuropathy in type 1 diabetes mellitus. *Diabetologia* 2004; 125: 1604-17.
18. Khurram M, Khar HB, Malik MF, et al. Evaluation of cardiac denervation in patients with long standing diabetes. *JCPSP* 2002; 12: 12-5.
19. Chen HT, Lin HD, Wong J G, et al. Cardiovascular autonomic neuropathic symptoms and diabetic complications in 674 type-2 diabetes. *Diabetes Res Clin Pract* 2008; 82: 282-90.
20. Camilleri M. Clinical practice Diabetic gastroparesis. *NEJM* 2007; 356: 820-9.
21. Ali ST, Rakkah NI. Neurophyiological role of sildenafil citrate (VIAGRA) on seminal parameters in diabetic males with and without neuropathy. *Pak J Pharm Sci* 2007; 20: 36-42.