

A STUDY OF PREVALENCE OF AUTONOMIC DYSFUNCTION IN TYPE-2 DIABETES MELLITUS IN A TERTIARY CARE CENTER

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ABSTRACT

BACKGROUND

Diabetes Mellitus, a disease characterized by hyperglycaemia caused by absolute or relative deficiency of insulin. The persistent hyperglycaemia causes a diverse functional and morphological alterations which affect almost all systems of the body. Although diabetic retinopathy, nephropathy and neuropathy are well known, autonomic neuropathy is the most neglected aspect of diabetic late complications due to difficulties in diagnosis, which requires invasive investigations in earlier days, and lack of specific treatment. This study has been conducted on the prevalence of autonomic dysfunction in Type II diabetes mellitus patients and the association of various factors with this disease in the diabetic population in and around Thanjavur.

Aims and objective of the study - 1) To study the prevalence of autonomic neuropathy in previously diagnosed and newly detected patients with Type 2 diabetes mellitus in Thanjavur. 2) To analyse the involvement of parasympathetic and sympathetic system in Type 2 Diabetes mellitus Patients with autonomic nervous system damage. 3) To find the correlation between autonomic impairment and proteinuria. 4) To establish the efficacy of the squatting test as an early marker of autonomic impairment.

MATERIALS AND METHODS

This is a prospective study and all the patients were admitted in Thanjavur medical college hospital and studied as in-patients. This study comprises of 40 Type 2 diabetes mellitus patients (26 males and 14 females). 10 healthy volunteers (relatives of patients), 6 males and 4 females were studied for age and sex matched control. The study duration is from January 2015 to August 2015 for a period of 8 months. The age range of study population varies from 40 years to 79 years. The duration of diabetes of the population studied ranges from 0 to 20 years. Newly detected as well as known diabetic patients were included in the study. By means of structured questionnaire, dizziness/vertigo/postural instability on standing, Regional hypohidrosis/hyperhidrosis, Dysphagia/vomiting/post-prandial gastric fullness/ nocturnal diarrhoea, diminished bladder sensation/decreased frequency of micturition, hesitation and weakness of urinary stream / urinary incontinence, impotence in males, tingling and numbness of extremities were asked aimed at assessing the presence of symptoms of autonomic neuropathy. Symptomatic autonomic neuropathy was considered to be present if one or more symptoms are present.

Seven cardiovascular autonomic tests were done to assess both sympathetic and parasympathetic function. Four tests evaluating parasympathetic, two tests evaluating sympathetic and one test evaluating both parasympathetic and sympathetic function. These tests are deep breathing test, heart rate response to standing, Valsalva manoeuvre, intravenous atropine, standing, sustained hand grip and squatting test. All ECGs were recorded in BPL Cardiart 108T/MK-vI ECG machine. Resting tachycardia and BMI are included in this study. The following are the biochemical tests such as Fasting Blood Sugar, Post Prandial Blood Sugar 2 hr after 75 gm of glucose load, Blood Urea, Serum Creatinine and 24 hrs Urinary Protein were done in the patients. Statistical association was calculated by using Chi-Square test.

RESULTS

90% of patients studied had prevalence of diabetic autonomic neuropathy. Parasympathetic involvement was seen in 82.5% of patients while sympathetic involvement was seen in 37.5%. Nocturnal diarrhoea and urinary symptoms had the greatest correlation with the severity of autonomic impairment. Among the tests performed, the heart rate response to deep breathing and to postural change from lying to standing were found to be the most sensitive in detecting prevalence of autonomic neuropathy. The squatting test may be used as an early marker of prevalence of subtle autonomic impairment, even in asymptomatic diabetics.

CONCLUSION

This study revealed a high prevalence of autonomic neuropathy in Type-2 diabetes mellitus patients. This was evident even in asymptomatic patients. The squatting test can be used as an early marker of dysautonomia. The degree of metabolic control was the factor which had the strongest association with severity of autonomic impairment. Thus, this study underscores the value of tight metabolic control in the ideal management of Type-2 diabetes mellitus.

KEYWORDS

Type 2 DM, Autonomic Dysfunction.

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BACKGROUND

The autonomic nervous system consists of two parts, the sympathetic system and parasympathetic system. The peripheral motor portion of the autonomic nervous system consists of preganglionic and postganglionic nerves. By means of electrophysiological testing, autonomic dysfunction can be seen in many diabetics without any other symptoms. Cardiovascular involvement is more common than any other system involvement. Postural hypotension is a late feature. Both afferent and/or efferent pathways may be affected. Cardiac parasympathetic function can be damaged without detectable sympathetic damage, but not the contrary.¹ Cardiac parasympathetic fibres are involved more expansively and earlier than sympathetic nerves. The autonomic symptoms are often imprecise and present insidiously, the bulk of diabetics with autonomic neuropathy may go undetected for a considerable time. Over a period of years, the symptoms may evolve into the elaborate picture of diabetic autonomic neuropathy which has been well detected since then accounted by Rundles² (1945), with a combination of other conditions like postural hypotension, nocturnal diarrhoea, gastric problems, bladder symptoms, abnormal sweating, impotence and a failure to detect hypoglycaemia.²

MATERIALS AND METHODS

This is a prospective study and all the patients were admitted in Thanjavur medical college hospital and studied as in-patients. This study comprises of 40 Type 2 diabetes mellitus patients (26 males and 14 females). 10 healthy volunteers (relatives of patients). 6 males and 4 females were studied for age and sex matched control. The study duration is from January 2015 to August 2015 for a period of 8 months. The age range of study population varies from 40 years to 79 years. The duration of diabetes of the population studied ranges from 0 to 20 years. Newly detected as well as known diabetic patients were included in the study.

Exclusion Criteria

Patients with,

- Coronary artery disease, cardiac arrhythmia, valvular heart disease and cardiac failure were excluded from the study.
- Previous history of myocardial infarction was excluded.
- Known hypertensive patients.

Financial or Other, Competing Interest: None.

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- Patients with airway disease were excluded.
- Patients with central and peripheral nervous system disease except those associated with Type 2 DM were excluded from the study.
- Patients who are on beta blockers, ACE inhibitors, calcium channel blockers, digitalis and other drugs likely to affect the autonomic function were excluded.
- Patients with any other chronic illness were also excluded.

By means of structured questionnaire like Dizziness/vertigo/postural instability on standing, Regional hypohidrosis/hyperhidrosis, Dysphagia/vomiting/post-prandial gastric fullness/ nocturnal diarrhoea, Diminished bladder sensation/decreased frequency of micturition, hesitation and weakness of urinary stream / urinary incontinence, Impotence in males, Tingling and numbness of extremities were asked aimed at assessing the presence of the following symptoms of autonomic neuropathy. Symptomatic autonomic neuropathy was considered to be present if one or more symptoms are present.

Seven cardiovascular autonomic tests were done to assess both sympathetic and parasympathetic function. Four tests evaluating parasympathetic, two tests evaluating sympathetic and one test evaluating both parasympathetic and sympathetic function. These tests are Deep breathing test, Heart rate response to standing, Valsalva manoeuvre, intravenous atropine, standing, sustained hand grip and Squatting test. All ECGs were recorded in BPL Cardiart 108T/MK-vI ECG machine. Resting tachycardia and BMI are included in this study. The following are the Biochemical tests such as Fasting Blood Sugar, Post Prandial Blood Sugar 2 hr after 75gm of Glucose load, Blood Urea, Serum Creatinine and 24 hrs Urinary Protein were done in the patients. Statistical association was calculated by using Chi-Square test.

Analysis of Grading of Dysautonomia

Grading of severity of autonomic neuropathy was done according to Lakhotia et al, 1997.³

Grading of dysautonomia according to Lakhotia et al 1997

Grade	Severity	Result of parasympathetic tests	Result of sympathetic tests
0	Normal sympathetic and parasympathetic functions	All normal or one Borderline	Normal
I	Mild parasympathetic dysautonomia	One abnormal or two borderline	Normal
II	Moderate parasympathetic dysautonomia	Two abnormal or one abnormal and two borderline	Normal
III	Severe parasympathetic dysautonomia	More than two abnormal results	Normal

IV	Combined parasympathetic and sympathetic dysautonomia	Any parasympathetic abnormality	One abnormal or two borderline
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RESULTS

Grade	Male	Female	Total
0	4 (10%)	0	4 (10%)
I	2 (7.7%)	3 (21.4%)	5 (12.5%)
II	10 (38.5%)	3 (21.4%)	13 (32.5%)
III	2 (7.7%)	1 (7.1%)	3 (7.5%)
IV	8 (30.8%)	7 (35%)	15 (37.5%)

Table 1. Gender Distribution with Respect to Grading of Dysautonomia

This above table shows increased incidence of grade 4 dysautonomia in both male and female diabetic population. (Table 1).

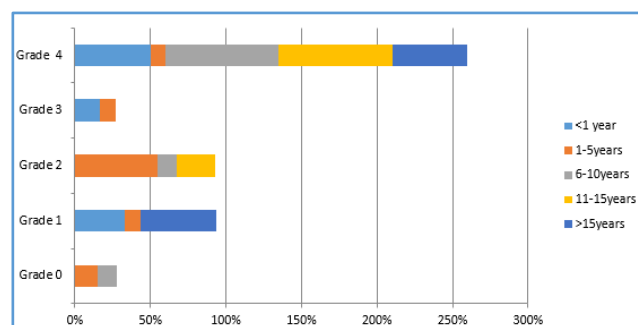


Figure 1. Grading of Dysautonomia and its Relation to Duration of Diabetes

This above chart shows increase in incidence of grade 4 dysautonomia in the population with greater than 10 years of duration of diabetes mellitus. (Fig. 1)

Symptom	Total No. s.	Grade 0	Grade I	Grade II	Grade III	Grade IV
Postural Hypotension	26 (65 %)	2	3	5	3	13
Gastric Fullness	28 (70 %)	2	4	8	2	12
Nocturnal Diarrhoea	4 (10 %)	0	1	0	0	3
Urinary Symptoms	10 (25 %)	1	1	3	0	5
Sweat. Abnormalities.	25 (62.5%)	1	3	7	1	13
Impotence	14 (35%)	2	0	7	0	5
Tingling & Numbness	28 (70 %)	1	3	7	3	14
Knee Jerk	5 (12.5%)	0	1	2	0	2
Ankle Jerk	16 (40 %)	0	1	8	1	6
Eye. Cataract	4 (10 %)	0	1	3	0	0
Eye NPDR	3 (7.5%)	0	0	1	0	2
Resting Tachycardia	13 (32.5%)	0	0	7	1	5

Table 2. Distribution of Number of Patients in Each Grade According to Autonomic Symptoms

This above table shows that there is increased prevalence of postural hypotension, gastric fullness, sweating abnormalities, paraesthesias, and resting tachycardia in the study group with grade 4 dysautonomia. (Table 2)

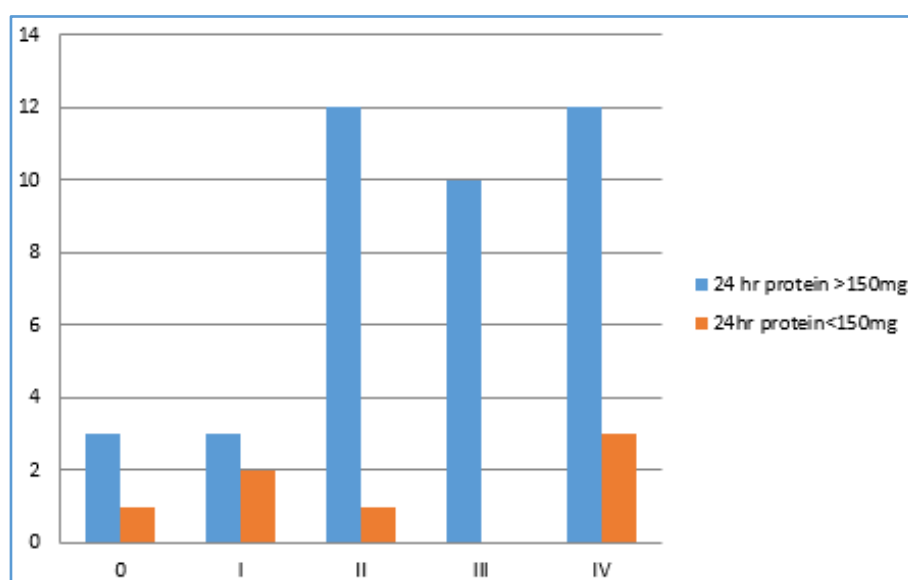


Figure 2. Distribution of Grades of Dysautonomia According to Proteinuria

This above chart shows that there is >150mg protein in urine /day in the study population with grade 2 and more than 2 dysautonomia. (Fig. 2)

Group	Test Result	Deep Breathing Test (n) %	30/15 Ratio (n) %	Atropine (n) %	PBT (n) %	HGT %	Valsalva Manoeuvre
Whole Group	Normal	(2) 5%	(17) 42.50%	(22) 55%	(16) 40%	(25) 62.50%	7 (17.5%)
	Borderline	(11) 27.50%	(0) 0%	(13) 32%	(14) 35%	(3) 7.50%	15 (37.5%)
	Abnormal	(27) 67.50%	(23) 57.50%	(5) 12.50%	(10) 25%	(12) 30%	18 (45%)
Males	Normal	(2) 7.60%	(13) 50%	(16) 61.50%	(13) 50%	(19) 73.10%	4 (15.4%)
	Borderline	(7) 26.90%	(0) 0%	(8) 30.80%	(8) 30.80%	(1) 3.80%	11 (42.3%)
	Abnormal	(17) 65.40%	(13) 50%	(2) 7.70%	(5) 19.20%	(6) 23.10%	11 (42.3%)
Females	Normal	(0) 0%	(4) 28.60%	(6) 42.90%	(3) 21.40%	(6) 42.90%	3 (21.4%)
	Borderline	(4) 28.60%	(0) 0%	(5) 35.70%	(6) 42.90%	(2) 24.30%	4 (28.6%)
	Abnormal	(10) 71.40%	(10) 71%	(3) 21.40%	(5) 35.70%	(6) 42.90%	7 (50%)

Table 3. Results of Cardiovascular Function Tests in Type-2 DM

This illustration shows that tests such as deep breathing tests are more yielding in detecting autonomic dysfunction. (Table 3)

Grade	Over Weight & Obese Nos. %		Non-Obese Nos. %	
0	1	25	3	75
I	3	60	0	40
II	1	7.7	12	92.3
III	0	0	3	100
IV	4	26.7	11	73.3

Table 4. Distribution of Grades of Dysautonomia in Relation to Body Mass Index

There was no statistically significant relation between the body mass index and dysautonomia. (Table 4)

DISCUSSION

This study was conducted on 40 Type 2 diabetic patients; 65% of them were males and 35% females. The mean age of the population studied was 55.4 ± 10.3 years, and the mean duration of diabetes was 5.2 ± 5 years. It has been advocated that a battery of tests is better in detecting the autonomic involvement than single test done (*123, Lakhota). In this study a battery of six autonomic function tests were performed to assess the integrity of both sympathetic and parasympathetic function. The duration of diabetes in most of the patients (50%) were in the group 1-5 years, 20% of the patients were in 6 - 10 years group, 10% patients were in the 11 - 15 years group, 15% of patients were in the <1-year group and only 2 (5%) patients in the >15 years group. The disease duration in the population studied ranges from <1 years to 20 years (fig. 1). It has been found in this study that 33 (82.5%) of patients studied had one or more autonomic symptoms suggestive of autonomic neuropathy and 7 (17.5%) of population did not have any symptoms of autonomic impairment. Among the seven asymptomatic patients, five had evidence of dysautonomia on testing. The presence of common symptoms such as impotence, postural dizziness and gustatory sweating^{4,5} which are commonly seen in diabetes do not essentially mean damage to the autonomic nervous system. In this study out of 26 patient who complained of postural dizziness only 34.6% had abnormal fall in systolic blood pressure 20 mmHg (table no. 2). The complaint of postural dizziness may be due to other causes. According to Ewing DJ, et al (1980) the presence of diabetic diarrhoea almost always indicates severe autonomic damage. In our study four patients had diabetic diarrhoea

and all of them were found to have severe autonomic dysfunction (grade IV). Out of 40 diabetic subjects 10 (25%) patients complained of symptoms suggestive of involvement of bladder, of which 9 (90%) had abnormal parasympathetic function tests and 5 had abnormal sympathetic tests. This is in agreement with Frimodt et al (1980)⁶ who described that infrequently seen symptoms like dysphagia or abnormal bladder are also indicative of widespread autonomic damage. A study of the various tests of autonomic functions showed that 82% patients had parasympathetic system involvement whereas only 37.5% had sympathetic involvement in the subjects studied. This observation is in agreement with that of Ewing DJ. et al⁷ and Banister R.⁸ who suggested that sympathetic involvement in the course of diabetic autonomic neuropathy occurs later than parasympathetic involvement. Among the individual tests of parasympathetic function, the greatest proportion of abnormal responses was seen in the deep breathing test (Beat to beat variation in the heart rate) in 27 patients (75%) (Table no. 3). This is followed by the lying to standing test (30th/15th Ratio) in 23 patients (63.8%), and finally the atropine test 5 patients (13.8%). Among the sympathetic tests the incidence of abnormality was 27.7% with sustained hand grip test and 33.3% with postural blood pressure test. This suggests that in clinical practice the deep breathing test and the hand grip test may be the most easily observable and reproducible tests to evaluate the abnormalities of parasympathetic and sympathetic function respectively. The novel squatting test described by Marfella et al⁹ combines both sympathetic and parasympathetic assessment in diabetic autonomic neuropathy in a single procedure. In our series 100% patients had abnormal parasympathetic component of the squatting test. It has been suggested by Marfella et al⁹ that the squatting test may be the earliest indicator of diabetic autonomic neuropathy. All patients tested in our study had an abnormal squatting test response, even among those who had no other evidence of diabetic autonomic neuropathy. The frequency of male and female distribution of autonomic dysfunction was 55% and 35% respectively (table no. 1). Out of 26 male patients studied 22.84% had autonomic dysfunction and all the female patients studied were found to have autonomic neuropathy. There was a highly significant sex difference in the distribution of classes of dysautonomia ($p < 0.001$). Results

of this study showed that 60% of patients had grade I autonomic neuropathy and 26.7% had grade IV dysautonomia in over weight and obese group (Body mass index >24.9.) In the non-obese group 40% of patients were found to be with grade 1 and 73.3% with grade IV autonomic impairment. This suggests that there exists no correlation between body mass index and severity of autonomic neuropathy (table no. 4). It has been found in this study 15 patients had grade IV autonomic impairment out of which 80% were in the proteinuria group (24-hour urine protein 150 mg) and only 20% were in the non-proteinuria group (24 hour urine protein 150mg). This is statistically significant ($p < 0.01$) suggesting that there exists a significant correlation between increased protein excretion and severity of autonomic damage (Fig. 2).

CONCLUSION

Parasympathetic involvement generally occurs earlier than sympathetic involvement. Evidence of autonomic dysfunction may be discovered even in asymptomatic patients by applying the tests described in the study. Nocturnal diarrhoea and urinary symptoms had the greatest correlation with the severity of autonomic impairment. Among the tests performed, heart rate response to deep breathing and to postural change from lying to standing were found to be the most sensitive in detecting autonomic neuropathy. The squatting test may be used as an early marker of prevalence of subtle autonomic impairment, even in asymptomatic diabetics.

However, a battery of tests is more accurate in assessing the degree of involvement of the autonomic system rather than a single test.

REFERENCES

- [1] Low PA, Walsh JC, Huang CY, et al. The sympathetic nervous system in diabetic neuropathy. A clinical and pathological study. *Brain* 1975;98(3):341-356.
- [2] Rundles RW. Diabetic neuropathy: general review with report of 125 cases. *Medicine* 1945;24(2):111-160.
- [3] Lakhota M, Shah PK, Vyas R, et al. Clinical dysautonomia in diabetes mellitus--a study with seven autonomic reflex function tests. *J Assoc Physicians India* 1997;45(4):271-274.
- [4] Ewing DJ, Campbell IW, Clarke BF. The natural history of diabetic autonomic neuropathy. *Q J Med* 1980;49(193):95-108.
- [5] Watkins PJ. Facial sweating after food: a new sign of diabetic autonomic neuropathy. *Br Med J* 1973;1(5853):583-587.
- [6] Fridodt-Moller C. Diabetic cystopathy: epidemiology and related disorders. *Ann Intern Med* 1980;92(2 Pt 2):318-321.
- [7] Ewing DJ, Clarke BF. Diagnosis autonomic neuropathy: a clinical viewpoint. In: Dyck PJ, Thomas PK, Asbury AK, et al, eds. *Diabetic neuropathy*. Philadelphia: WB Saunders 1987:66-88.
- [8] Bannister R. Primary autonomic failure and classification of diseases of the autonomic nervous system. In: Thomas PK, ed. *New Issues in Neurosciences. Autonomic Neuropathies*. Vol. 1. Chichester: John Wiley 1989:267-276.
- [9] Marfella R, Giugliano D, di Maro G, et al. The squatting test. A useful tool to assess both parasympathetic and sympathetic involvement of the cardiovascular autonomic neuropathy in diabetes. *Diabetes* 1994;43(4):607-612.