Autonomic manifestations in diabetes mellitus: A case control study in rural population

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Abstract
Autonomic dysfunction is one which is often a disabling complication of Diabetes Mellitus. Failure to recognize the symptoms in a diabetic autonomic dysfunction may lead to a substantial morbidity and mortality, however insidious the onset may be. Thus, knowing its importance, this study features the various clinical manifestations of Autonomic Dysfunction in Diabetes, in the rural area, and by simple bedside tests. This study aims to detect cases of autonomic dysfunction and its significant correlation with Diabetes. This study was carried out on 50 patients with Diabetes Mellitus and 50 healthy controls. Autonomic function bedside tests were conducted on all study participants and the autonomic scores were calculated. Electrocardiograms were taken to calculate the corrected QT-interval. Glycemic profile was measured in all the subjects. Comparison of these parameters were done between the Diabetic and control group. Significant positive autonomic scores were observed in all the tests in diabetic group when compared to the study group. Impotence (36%), postural giddiness (30%) and sweating disturbances (26%) were the common symptoms noted among the diabetic group. Prolonged QTc interval of value greater than >0.44 was seen in 18 subjects (36%) in the diabetic group where it is seen only in 4 subjects (4%) in the control group. Among the diabetic group mean HbA1c for those with negative autonomic scores was 5.98±1.41% as compared to 7.24±2.42% with positive autonomic scores. Thus, there is an increased incidence of autonomic dysfunction among diabetic patients. The increased autonomic scores are suggestive of the same.

Keywords: Autonomic function tests, Diabetes Mellitus, HbA1c, QT interval, Autonomic neuropathy.

Introduction
India is the diabetic capital of the world. Diabetes is definitely a growing menace in our society, with a growing worldwide incidence. Diabetes is continued to be known to man for centuries but yet to be fully understood. The number of people with diabetes has increased alarmingly since 1985. In 1985, an estimated 30 million people world-wide had diabetes; by 2003, it was estimated that approximately 194 million people had diabetes, and this figure is expected to rise to almost 350 million by 2025.[1] To beat it all, though diabetes can be easily detected and diagnosed overall, it's actual 'hold' over the various systems in the form of complications are seldom fully recognized. Most people link diabetes to major manifestations of the eyes or heart that they overlook its grasp on the nerves, and the dreaded neuropathic complications. All forms of diabetes are characterized by hyperglycemia, due to relative or absolute lack of insulin or the malfunctioning of insulin. This hyperglycemia progresses onto the development of diabetes-specific microvascular pathology in the retina, glomerulus, and peripheral nerves.[2] Autonomic dysfunction is another disabling complication in diabetics.

Significance of autonomic dysfunction in Diabetes is huge as it has 5-year mortality of 50%, it is common cause of sudden death, has been correlated with greater complications after elective surgery and increased danger with general anesthesia.[3] The significant increase in major microvascular complications makes it important to screen diabetes at a younger age of 45 years. Failure to recognize the symptoms in a diabetic, as due to autonomic dysfunction and later lead to lot of unnecessary investigations and wasteful treatment. Thorough understanding of diabetic autonomic dysfunction on the various systems is necessary.[4]

Common clinical presentations with autonomic dysfunctions are postural hypotension, gastrointestinal disturbances, sweating abnormalities, bladder dysfunction, erectile dysfunction and other symptoms.[5,6] Among these complications, cardiac manifestation seems to more common and dreadful. Autonomic nerves provide the heart with very fine control mechanism; variations in vagal tone very rapidly alter heart rate on a beat-to-beat basis while stimulation of the sympathetic tone has a more gradual accelerator effect. There are several investigations to assess the cardiac autonomic functions. Heart rate variability in most widely accepted predictor of functional status of the heart. The actual measurement of heart rate variability has been achieved via multiple different modalities. It is usually calculated by analyzing the time series of beat-to beat intervals from ECG or arterial pressure tracings, i.e. standard deviation of beat-to-beat intervals. It consists of time domain and frequency domain parameters. Other conventional tests are generally used to measure cardiac autonomic function tests are recording the heart rate and blood pressure changes during maneuvers.[7,8] The objective of the study was to observe the presenting manifestations of autonomic dysfunction in diabetes mellitus and compare it with the normal subjects.

Materials and Methods
The study was conducted in patients who presented in the OPD of General Medicine in the rural medical college. The Institutional ethical clearance was obtained for the study. The study was conducted in November, 2008 to April, 2010. Diabetic group consisted of 50 subjects who were randomly selected and consisted of 34 males and 16 females. The study also involved 50 controls, i.e. non-diabetic patients. Inclusion criteria for the diabetic group are patients with fasting (of more than 8 hours) blood glucose levels of more than 126

mg/dl and/or two-hour Post-prandial blood glucose levels of more than 200 mg/dl.[9-10] Patients with severe anemia, congestive cardiac failure, gross nutritional deficiency, exposure to alcohol, lead, neurotoxic drugs (like INH) and drugs affecting the autonomic function, renal failure, on anti-hypertensive medication, Chronic obstructive lung disease, Central or peripheral neuropathies due to cause other than Diabetes, Liver Diseases, Cardiac arrhythmias were excluded from the study.

The selected 50 Diabetic patients were questioned about the presence of symptoms reported to be related to autonomic neuropathy, viz. postural giddiness, and nocturnal polyuria, disturbances of bladder sphincter, constipation, diarrhea, impotence and bouts of localized sweating. All the patients were subjected to a detailed clinical examination. Glycosylated hemoglobin levels were assessed in all the subjects. The following tests were performed to assess the autonomic functions in the above patients.[11-12] Tests reflecting parasympathetic function and sympathetic functions are listed in the Table 1 with their scoring system.[13]

Heart rate variation during deep breathing

Deep breathing, at six breaths a minute, is the most convenient and reproducible technique. The patients breathe deeply at six breaths a minute (five seconds in and five seconds out) for one minute. An electrocardiogram is recorded throughout the period of deep breathing, with a marker used to indicate the onset of each inspiration & expiration. The shortest R-R interval during inspiration and longest R-R interval during expiration was measured to calculate the difference in heart rate.

Heart rate response to Valsalva maneuver

The patient is asked to blow into the sphygmomanometer tube to maintain a pressure of 40 mm of Hg for 15 seconds, with continuous recording of electrocardiogram. During each maneuver, the electrocardiogram is recorded during the strain, and for 15 seconds following the release. The results are expressed as Valsalva ratio, which is the ratio of longest R-R interval after the maneuver to the shortest R-R interval during the maneuver.

Immediate heart rate response to standing

During the change of position from lying to standing a characteristic immediate rapid increase in heart rate occurs, which is maximal at about the 15th beat after standing. A relative overshoot bradycardia then occurs, maximal at about the 30th beat. This response is mediated by the vagus nerve. The test is performed with patient lying quietly on a bed, while the heart rate is recorded continuously on an electrocardiograph. The patient is asked to stand up unaided and the point, at which the patient starts to assume an erect posture, is marked on the electrocardiogram. The shortest R-R interval at around the 15th beat and longest R.-R interval at around 30th beat are measured. The characteristic heart rate response is expressed by the 30.15 ratio.

Blood pressure response to standing

The test is performed by measuring the patient's blood pressure while he is lying down quietly, and after he stands up at one minute intervals. Three readings were obtained, and the average drop in the systolic blood pressure was taken.

Blood pressure response to sustained handgrip

The patients were asked to maintain 1/3rd of maximal voluntary contraction for 5 minutes, and blood pressure is recorded in the non-exercising arm, at rest, and during one-minute interval during the grip. The result is expressed as the difference between the highest diastolic blood pressure during the handgrip, and the mean of the three diastolic blood pressure readings, before the handgrip began.

A corrected QT interval (QTc interval)

Resting ECG is recorded in all the patients and QT interval in seconds is detected. The QTc interval (in seconds) = QT interval (in seconds)/ √R-R interval (in seconds) (13). Based on the results of the above tests, the autonomic manifestations in diabetics were ascertained, and further analyzed using statistical test, student t test.

Results

Total of 100 subjects participated the study with 50 subjects each in diabetic and control group. Impotence is the commonest symptom of autonomic dysfunction and polyneuropathy the commonest complication with the incidence of 36% in the diabetic group. The other common symptoms are sweating disturbances (26%), postural giddiness (30%). The occurrence of symptoms between diabetic group and control group is compared and presented in the Table 2. Incidence of cataract in the diabetic group was 20% and in control group was 12%. The average of participants in the study was 54.43±15.12 years and the mean duration of diabetic in the participants was 10.96±6.95 years.

Table 1: Normal, borderline and abnormal values in tests for autonomic functions

Tests	Normal values	Borderline values	Abnormal values
A. Parasympathetic Function Tests			
1. Heart rate variation during deep breathing (beats/min)	15 or more	11-14	10 or less
2. Immediate heart rate response to standing (30:15 ratio**)	1.04 or more	1.01-1.03	1.00 or less
3. Heart rate response to valsalva maneuver (valsalva ratio*)	1.21 or more	1.11-1.20	1.10 or less
B. Sympathetic Function Tests			

1. B.P response to standing (fall in systolic blood pressure) (mm of Hg)	10 or less	11-29	30 or more
2. B.P response to handgrip (increase in diastolic blood pressure) (mm of Hg)	16 or more	11-15	10 or less
Scores*	0	1	2
*Of total sum of 10, if total score obtained from tests is >5, i.e 6 or above, it is considered positive autonomic Score			

Table 2: Presenting complaints among the diabetic and control group

Presenting complaints	Diabetic Group (n=50)		Control Group (n=50)		P value
	No	%	No	%	
Postural giddiness/syncope	15	30.0	2	4.0	0.001**
Constipation	10	20.0	0	0.0	0.001**
Diarrhea	4	8.0	5	10.0	1.000
Sweating disturbances	13	26.0	0	0.0	<0.001**
Pupillary changes	9	18.0	0	0.0	0.003**
Bladder disturbances	10	20.0	0	0.0	0.001**
Urinary tract infections	5	10.0	1	2.0	0.204
Impotence	18	36.0	0	0.0	<0.001**
Cholelithiasis	8	16.0	3	6.0	0.110
Cataract	10	20.0	6	12.0	0.275
Dermopathy	5	10.0	0	0.0	0.058+
Ulcers on foot	10	20.0	0	0.0	0.001**
Pulmonary tuberculosis	2	4.0	2	4.0	1.000

The heart rate and BP responses in the two group in depicted in Table 3. Significant positive autonomic cardiovascular reflex tests among diabetic group than control group. Autonomic scores were compared between the groups and there statistically more significant positive autonomic scores in diabetic group than control group. The results are depicted in Fig. 1 and Table 4.

Table 3: Comparison of Heart rate and BP response in two groups of patients

	Diabetic group	Control group	P value
Heart rate response to deep breathing	12.26±4.95	21.04±5.26	<0.001**
Heart rate response to valsalva maneuver	1.07±0.27	1.28±0.19	<0.001**
Immediate heart rate response to standing	1.01±0.15	1.27±0.19	0.001**
B.P response to standing	14.88±7.51	10.96±9.31	0.030*
B.P response to handgrip	14.40±5.57	18.24±3.95	<0.001**

Table 4: Distribution of Autonomic scores among the subjects

Autonomic score	Diabetic group		Control group	
	No	%	No	%
Negative (<=5.0)	22	44.0	44	88.0
Positive (>5.0)	28	56.0	6	12.0
Total	50	100.0	50	100.0
Inference	Autonomic positive cases are significantly more in Cases compared to Controls with P<0.001**			

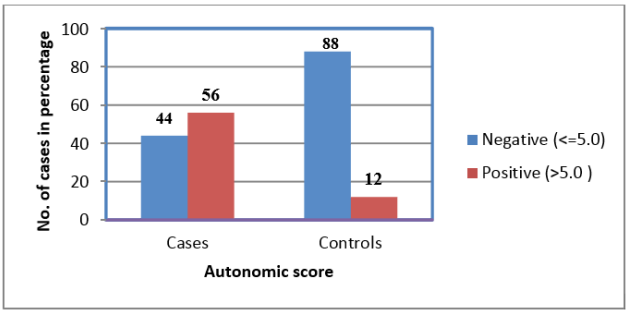

Fig. 1: Distribution of Autonomic scores among the subjects

The Mean corrected QT interval (QTc) is 0.419 ± 0.05 seconds in the diabetic group and 0.394 ± 0.04 seconds in the control group. The statistically significant difference between diabetic and control group with p=0.003*. QTc interval of value greater than >0.44 was seen in 18 subjects (36%) in the diabetic group where it is seen only in 4 subjects (4%) in the control group. Comparison of Corrected QTc intervals by

E.C.G (in seconds) in two groups of patients is depicted in Table 5.

Table 5: Comparison of Corrected QTc intervals by E.C.G (in seconds) in two groups of patients

Corrected QT Interval	Diabetic Group (n=50)	Control Group (n=50)
0.35-0.40	25(50.0%)	34(68.0%)
0.41-0.45	7(14.0%)	12(24.0%)
0.46-0.50	18(36.0%)	4(16.0%)
Mean ± SD	0.419±0.05	0.394±0.04
Inference	Corrected QTC interval is significantly increased in Cases with P=0.003**	

Mean Glycosylated Haemoglobin (HbA1c) was in the diabetic group was 8.24±2.59%. Mean HbA1c was 7.24±2.42% in the subjects with positive autonomic scores and it was 5.98±1.41% in subjects with negative autonomic scores.

Discussion

Incidence of varied symptoms of autonomic dysfunction in diabetic group is described as follows. In this study, 46 out of the 50 diabetes patients studied, presented with symptoms suggestive of autonomic neuropathy in the form of impotence, postural giddiness, constipation, sweating disturbances, bladder disturbances and diarrhea. Impotence was the most common symptom in this study. It was encountered in 18 out of the 50 patients (36%). Out of this, it was encountered in 10 out of the 34 males, mainly in the form of erectile dysfunction. Rundles[14] found impotence in 19 patients out of 125 diabetic patients. Noronha JL et al[15] found impotence in 52% of their study diabetic subjects, being the commonest symptom. Gupta et al[16] in their study found 12 patients with impotence in 50 diabetic patients.

Postural giddiness was the next common symptom seen in 15 out of the 50 diabetic patients (30%). This is statistically significant. The findings in this study were similar to that of Nijhawan et al[17] who found an incidence of 28% (7 out of 25 patients). Goel A et al[18] in their observation, have made a fact that postural giddiness, is the commonest symptom (21.3%), others being impotence (9.3%), diarrhea (9.3%), abnormal sweating and dysphagia. Sweating disturbances in the form of decreased sweating were seen in 26% of the patients - 13 out 50 diabetics. No control had symptoms of sweating disturbances, making this a significant symptom of autonomic neuropathy. Bladder disturbances, in the form of incontinence and retention of urine, were seen in 10 out of 50 patients (20%). Rundles[14] observed 32 out of 125 diabetics (25.6%) with bladder disturbances while Gupta et al[16] observed bladder disturbance in 5 out of 50 diabetics (10 %).

Constipation was also a common symptom seen in 10 out the 50 diabetic patients (20%). Aaron I et al[19] says that constipation is the most common lower G.I symptom in diabetics. Diarrhea, which was nocturnal, profuse and watery, was seen in 4 out of the 50 diabetic patients (8%). Rundles[14] reported 21.6% patients with diarrhea - 26 out of 125 patients, Chowdary D et al[20] in their update article on "Approach to case of Autonomic Neuropathy", states that diabetes mellitus is the most important cause of autonomic neuropathy. Autonomic features, which involve the cardiovascular, gastrointestinal, urogenital, sudomotor and pupillomotor systems, occur in varying combinations, of which, orthostatic hypotension is often the first recognized and most disabling symptom.

Comparison of autonomic dysfunction in diabetic group and control group is described as follows. Ewing's autonomic test scoring system as used to evaluate if a patient had autonomic dysfunction. This system is described in the methods. It has maximum total score of 10 to a minimum of 0, a score of more than 5, i.e. 6 or more was considered as positive autonomic scores. Among the 50 diabetic patients, 28 patients had positive Autonomic scores (56%). Only 6 among 50 controls had an autonomic score of more than 5, indicating a strong association between autonomic dysfunction and its manifestations in diabetes. The incidence of autonomic neuropathy in diabetics, ranged from 17 to 68% in other studies. Pappachan M[21] et al in their study, showed a prevalence of cardiovascular autonomic neuropathy in 60% of the 100 cases of diabetics studied. Goel A et al[18] have reported 29 out of 75 diabetic patients (39%) to have dysautonomia. Similar results were seen with Oluranti B. Familoni et al[22] have showed a prevalence of 37% of dysautonomia among the diabetics under study.

Duration of diabetes vs incidence of autonomic dysfunction

The incidence of autonomic neuropathy increased with the increasing duration of diabetes. Among those with positive autonomic scores, the average age was 54.43±15.12 years as compared to 42.91±12.59 years in those with negative scores, indicating the increased prevalence of autonomic dysfunction in diabetics among the older age groups. Also we see that in those cases that had positive autonomic scores, the average duration of diabetes was 10.96±6.95 years as compared to 5.39±3.06 years in those who had negative scores. This clearly indicates the correlation between increasing duration of diabetes and the occurrence of autonomic neuropathy. Roy Freeman et al[23] reported an incidence of 15% autonomic neuropathy in diabetics of duration up to 10 years and 62% in diabetics of more than 10 years.[9] Lakhotia M et al[13] showed a great incidence of dysautonomia with increasing duration (up to 80% in those with duration of more than 5 years).

Glycemic control and autonomic dysfunction

Poor glycemic control is associated with diabetic complications and notably with autonomic neuropathy. The mean value of glycosylated hemoglobin in most of these patients at the time of recruitment for study was 7.24±2.42%. It was noticed that the cases with positive autonomic scores had uncontrolled blood sugars (fasting and post-prandial blood sugars) than those with negative scores. Among the cases, those with positive scores had a mean value of glycosylated hemoglobin of 8.24±2.59% as against that of 5.98±1.41% in those with negative scores. The target

glycosylated haemoglobin in normal individuals is 7.0%, and for diabetics is 6.5%.[21] This clearly indicates that these patients had a poor glycemic control over the previous 3 months or more, also indicating the significant correlation between poor glycemic control and prevalence of diabetic autonomic neuropathy. Pappachan JM et al[21] in their study, also showed that incidence of diabetic autonomic neuropathy increased with increasing duration and poor glycemic control. Gupta RC et al[16] studied cardiovascular reflexes after 6 months of strict metabolic control and found that 22% patients showed significant symptomatic improvement and 18% showed improved test score.

Sympathetic v/s parasympathetic tests

In the present study, the tests used to evaluate parasympathetic system where found to be more sensitive indicators of autonomic neuropathy. More than 80% of the diabetics with positive autonomic scores had at least one parasympathetic test abnormal or borderline, and at least 60% had at least two tests abnormal or borderline. Goel A et al[18] observed that 50% of the diabetics with dysautonomia had both abnormal sympathetic and parasympathetic tests. Noronha JL[15] reported 45.5% of their diabetic subjects had inadequate heart rate response to standing. In this study, 48% cases had abnormal or borderline values for the heart rate response to standing, results almost matching with their study.

Corrected QT interval in E.C.G. v/s Diabetic Autonomic Neuropathy

A corrected QT interval of more than 0.44 seconds was present in diabetic autonomic dysfunction and was more prominent in cases with significant risk factors, like advanced age, longer duration and peripheral neuropathy. In this study, it was ascertained that the corrected QT interval was statistically significantly increased among diabetic cases compared to controls. Oluranti B. Familoni et al[22] showed a prevalence of 30% of diabetic autonomic neuropathy in the cases with prolonged corrected QT interval. Pappachan JM et al[21] in their study, showed a significant association between CAN and prolonged corrected QT interval (OR 5.55s). Roy Freeman, in his article, "Autonomic peripheral neuropathy", Roy Freeman 2005[23] says that mortality in diabetics due to cardiovascular autonomic neuropathy is 27-56% in 5-10 years period.

Conclusion

There were increased number of abnormal parasympathetic (heart rate variability) tests as compared to sympathetic (blood pressure variability) tests. There was a statistically significant effect of duration of disease and glycemic state (based on fasting blood sugar/ post-prandial blood sugar/ HbA1c) on autonomic neuropathy among the cases. There were statistically significant prolongations in corrected QT-intervals in diabetics compared to controls. It is necessary to anticipate the early autonomic dysfunction in diabetic patients and accord necessary treatment.

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Conflict of interest

None.

References

1. Michael Brownlee, Lloyd. P. Aiello, Mark E. Cooper, William's textbook of Endocrinology, 11th edition, chapter 32, 1418-1490.
2. Tarsy Daniel, Freeman Roy. "The nervous system and diabetes", Joslin'. Diabetes mellitus, 13th edition 794-798.
3. Harrison's Principles of Internal Medicine, Autonomic Neuropathy in Diabetes Mellitus, Chapter 338, 17th edition, pg.2289-2293.
4. Michael E. Farkouh, Elliot J. Rayfield, Valentin Fuster: "Diabetes and Cardiovascular disease" Hurst's The Heart, 12th Edition, pp 2073-2103.
5. Adams D Raymond, Victor Morris; Principles of Neurology, 9th edition, pp 505-527.
6. API Textbook of Medicine, Diagnosis of Diabetes Mellitus, 8th edition, vol. 2, pages 1049-1051.
7. Suraj Kupa, Virend K. Somers, "Cardiovascular manifestations of Autonomic Disorders", Braunwald's Heart Disease: A textbook of Cardiovascular Diseases, 8th Edition, WB Saunders, 2008, pp 2171-2183.
8. Robertson RH, Robertson D. "Cardiovascular manifestations of Autonomic Disorders", Braunwald's Heart Disease: A textbook of Cardiovascular Diseases, 7th Edition, WB Saunders, 2008, pgs 2173-2184.
9. American Diabetes Association Standards of medical care in diabetes—2007. *Diabetes Care* 2007;30 (Suppl 1):S4-S41.
10. Gabir MM, Hanson RL, Dabela D. The 1997 American Diabetic Association and 1999 World Health Organization criteria for hyperglycemia in the diagnosis and prediction of diabetes. *Diabetes Care* 2000;23:1108-1112.
11. Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. *Br Med J* 1982;285:916-8.
12. Ewing DJ, Campbell IW, Murray A, Neilson JMM, Clarke BF. Immediate heart-rate response to standing: simple test for autonomic neuropathy in diabetes. *Br Med J* 1978;1:145-7.
13. Lakhotia M, Shah PKD, Vyas R, Jain SS, Yadav A, Parihar MA. Clinical dysautonomia in diabetes mellitus- A study with seven autonomic reflex function tests. *JAPI* 1997;45:4.
14. Rundle RW. Diabetic neuropathy. Medicine (Baltimore) 1945;24:111-60.
15. Noronha JL, Bhandarkar SD, Shenoy PN, Retnam VJ. Autonomic neuropathy in diabetes mellitus. *J Postgrad Med* 1981;27:1-6.
16. Gupta RC, Chittora MD, Jain A. a study of autonomic neuropathy in diabetes mellitus in relation to its metabolic control. *JAPI* 1995;43(7):1-3.
17. Nijhawan S. Autonomic and peripheral neuropathy in insulin dependent diabetes. Joint Association of Physicians of India 1993;41(a):565-6.
18. Goel A, Ruchika Agarwal, Singla S, Lakhani KK, Sonigra DT, Agarwal SB. A clinical study on Autonomic nervous system manifestations in Diabetes mellitus. *J Assoc Physicians India* 2005;53:999.
19. Aaron I. Vinik, Raelene E. Maser, Braxton D. Mitchell, Roy Freeman. Diabetic Autonomic Neuropathy. *Diabetes Care* 2003;26(5):1553-79.
20. Chowdary D, Patel N. Update article on approach to a case of autonomic peripheral neuropathy. *JAPI* 2006;54:727.
21. Pappachan M, Sebastian J, Bino BC. Cardiac autonomic neuropathy in diabetes mellitus: prevalence, risk factors and utility of corrected QT interval in the ECG for its diagnosis. *Postgrad Med J* 2008;84(990):205-10.

22. Oluranti B. Familoni, Olatunde Odusan, Taiwo H. Raimi. The relationship between QT intervals and cardiac autonomic neuropathy in Nigerian patients with type 2 diabetes mellitus. *Nigerian Med Pract* 2008;53(4):48-51.
23. Roy Freeman. Autonomic peripheral neuropathy. *Lancet* 2005;365:1259-70.