Original Research Paper

Internal Medicine

ASSESSMENT OF CARDIAC AUTONOMIC NEUROPATHY IN PATIENTS WITH TYPE-2 DIABETES MELLITUS

Vivek Agarwal*	Assistant Professor, Department of Medicine, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India. *Corresponding Author
Archana Garg	Associate Professor and Unit Head, Department of Ophthalmology, J L N Medical College and Hospitals, Ajmer, Rajasthan, India.
Mahendra Khanna	Associate Professor, Department of PSM, J L N Medical College and Hospitals, Ajmer, Rajasthan, India.

ABSTRACT   **Introduction:** Cardiovascular autonomic neuropathy (CAN) is an "impairment of cardiovascular autonomic control in patients with established diabetes after excluding other causes. Autonomic nerve fibers innervate the heart and blood vessels, in turn causing abnormalities in heart rate and vascular dynamics. It is known to affect multiple organ systems and is a major cause of morbidity and mortality in patients with diabetes. **Methodology:** A descriptive observational study was conducted after obtaining required approvals and consent from patients; from September 2015 to December 2016 at Santokba Durlabhji Memorial Hospital, Jaipur. 60 NDDM subjects 45 male and 15 female aged 40-60 years attending OPD of ……….. medical college…… and 30 controls with 22 males and 8 females were taken. The age and sex of both groups were matched. Other causes of autonomic neuropathy were excluded from study subjects by taking proper history and general clinical and lab investigations. **Results:** A total of 60 NIDDM subjects 45 male and 15 female mean age 48.34+ 8.42 years and 30 controls with 22 males and 8 females mean age 51.75+ 5.30 were taken. In NIDDM subjects parasympathetic test results for E:I test was 1.17+0.12, 30:15 test was 1.03+0.10 and V/R test was 1.23+0.16. While in control subjects results were 1.30+0.08, 1.19+0.05, and 1.42+0.03. In NIDDM subjects, sympathetic test results for postural hypotension were 46.20+2.41, hand grip test was 14.12+2.13, and cold pressure test was 9.12+2.16. While in control subjects results were 12.08+8.72, 16.44+3.25, 15.36+4.33. The prevalence of CAN in a total 60 NIDDM patients was 40 (67.5%). **Conclusion:** As a single test E:I ratio was found to be the best predictor of CAN parasympathetic division. Dual combination of E:I and VR ratio test was found to be the best predictor of CAN giving maximum yield. The hand grip test was the best predictor of CAN sympathetic division.

INTRODUCTION:

Cardiovascular autonomic neuropathy (CAN) is a microvascular complication defined as the impairment of cardiovascular autonomic control in persons with diabetes, with no other causes[1]. The prevalence of CAN varies from nearly 2% in patients with newly diagnosed or well-controlled diabetes, up to 60% of patients with long-standing type 2 diabetes mellitus, and 90% of pancreas transplantation candidates with type 1 diabetes[2,3]. The CAN Subcommittee of Toronto Consensus Panel on Diabetic FHNeuropathy defines CAN as an "impairment of cardiovascular autonomic control in patients with established diabetes after excluding other causes."[4,7] Diabetes-associated cardiovascular autonomic neuropathy (CAN) damages autonomic nerve fibers that innervate the heart and blood vessels, in turn causing abnormalities in heart rate and vascular dynamics. It is known to affect multiple organ systems and is a major cause of morbidity and mortality in patients with diabetes.[4-7] Significantly underdiagnosed, CAN exhibits multiple clinical manifestations, such as orthostasis, resting tachycardia, exercise intolerance, silent myocardial infarction, and intraoperative cardiovascular liability. It is a severely debilitating complication that often decreases survival in patients with diabetes.[4,8]

OBJECTIVES:

Assessment of cardiac autonomic neuropathy (CAN) in type 2 diabetes mellitus subjects by using standardized non-invasive cardiovascular reflex test.

MATERIALS AND METHODS:

A descriptive observational study was conducted after obtaining required approvals and consent from patients; from September 2015 to December 2016 at Santokba Durlabhji Memorial Hospital, Jaipur. 60 NDDM subjects 45 male and 15 female aged 40-60 years attending OPD of ……….. medical college…… and 30 controls with 22 males and 8 females were taken. The age and sex of both groups were matched. Other causes of autonomic neuropathy is excluded from study subjects by taking proper history and general clinical and lab investigations.

Test reflected parasympathetic dysfunction:
* Deep breathing test (E:I ratio) = maximum RR interval during expiration divided by same for inspiration.
* Heart rate response to lying to standing test (30:15 ratio)= maximum RR interval around 30th beat divided by same for 15th beat.
* Valsalva test (V/R ratio): largest divided by the shortest RR interval during maneuver

Test reflecting sympathetic dysfunction:
* Lying to standing test (postural hypotension test)
* Hand grip test
* Cold pressure test

RESULTS:

60 NIDDM subjects 45 male and 15 female mean age 48.34+ 8.42 years and 30 controls with 22 males and 8 females mean age 51.75+ 5.30 were taken. In NIDDM subjects parasympathetic test results for E:I test was 1.17+0.12, 30:15 test was 1.03+0.10 and V/R test was 1.23+0.16. While in control subjects results were 1.30+0.08, 1.19+0.05 and 1.42+0.03. In NIDDM subjects, sympathetic test results for postural hypotention was 46.20+2.41, hand grip test was 14.12+2.13, and cold pressure test was 9.12+2.16. While in control subjects results were 12.08+8.72, 16.44+3.25, 15.36+4.33. Prevalence of CAN in total 60 NIDDM patients were 40 (67.5%).

DISCUSSION:

Dysautonomia has been widely studied in the past in patients of diabetes. Some prominent studies focused on detection of this abnormality in patients of IDDM while others compared autonomic dysfunction in relation to peripheral nervous system involvement. The present study is directed toward the detection of dysautonomia in type 2 diabetic subjects and evaluation of non-invasive tests deciding the best predictor value for autonomic dysfunction in these subjects. In this study prevalence of CAN was found to be 67.5% by using 6 cardiovascular reflex tests. Parasympathetic dysfunction (53.25%) was more prevalent than sympathetic dysfunction (26.25%). This goes along with the regular observation that parasympathetic involvement occurs much earlier in course of NIDDM, sympathetic system is involved late and it's dysfunction indicates grave prognosis. Prevalence of CAN increases with increasing age and duration of diabetes, but this observation was not statistically significant.

In this study cardiovascular reflex test E:I ratio was found to be the best predictor of CAN giving rise to maximum yield in most subjects. About 37% of diabetic subjects have an abnormal E:I ratio (≤1.10). A study by Tandon et al.[9] reported prevalence of abnormal E:I ratio in

39.5% of subjects and by Lakhotia et al.[10] reported 42% prevalence.

Valsalva ratio test was analysed as the second best CVR test for detecting clinical dysautonomia. This VR ratio test has been considered reflex heart rate control mechanism which is usually affected by CAN in diabetic subjects. In this study, 35% of diabetic patients have an abnormal value of V/R ratio (≤1.10), while a study by Sharpey et al.[11] reported prevalence of abnormal VR ratio in 21% of diabetic subjects. A study by Tandon et al.[9] reported abnormal VR ratio prevalence in 39.5% subjects while a study by Lakhotia et al.[10] reported 20% prevalence.

We concluded from present work that autonomic nervous system dysfunction is a common entity in apparently uncomplicated diabetes. Tests though can be performed for both parasympathetic and sympathetic dysfunction but significant detection of patients is largely possible by utilization of tests for parasympathetic dysfunction. The test appearing best for this abnormality is E:I ratio as a single test that has reported maximum prevalence (37%).

The important observation of this study is a combination of 2 non-invasive tests i.e. (E:I and VR ratio) resulting in detection of maximum number of patients with clinical dsyautonomia.

CONCLUSION:
A total of 60 NIDDM subjects were subjected to 6 cardiovascular reflex tests 40 NIDDM subjects were found to have one or more abnormal CVR tests indicating dysfunction and 20 had autonomic dysfunction. Overall parasympathetic dysfunction was 53.25%, overall sympathetic dysfunction was 26.75%, both parasympathetic and sympathetic dysfunction were 12.50%, and overall prevalence of CAN was 67.5%.

When compared with control all NIDDM subjects have significantly lower CVR values than control group indicating involvement of the autonomic nervous system.

As a single test - E:I ratio was found to be the best predictor of CAN parasympathetic division. Dual combination of E/I and V/R ratio tests was found to be the best predictor of CAN giving maximum yield. Hand grip test was the best predictor of CAN sympathetic division.

Prevalence of cardiac autonomic neuropathy increases with increasing age of diabetic subjects. There is a slight male preponderance in diabetic subjects with CAN in each age group. Prevalence of CAN increases with increasing duration of diabetic mellitus.

Table 1: Normal, Borderline And Abnormal Values Of The Test

Name of test	Normal	Borderline	Abnormal
Valsalva ratio	≥1.21	1.11-1.20	≤1.10
E:I ratio	≥1.21	1.11-1.20	≤1.10
30:15 beat ratio	≥1.04	1.01-1.03	≤1.00
Postural hypotension	≤10 mm	10-29 mm	≥30 mm
Increase in Diastolic BP after sustain handgrip / cold pressure test	≥16 mm	11-15 mm	≤10 mm

Table 2: Distribution Of Test Results In NIDDM Subjects (n=60).

Name of test	Normal	Borderline	Abnormal
Valsalva ratio	33 (55%)	6 (10%)	21 (35%)
E:I ratio	28 (46%)	10 (17%)	22 (37%)
30:15 beat ratio	38 (62.5%)	5 (10%)	17 (27.5%)
Postural hypotension	40 (66.6%)	12 (20%)	8 (13.3%)
Handgrip test	38 (64.25%)	9 (15%)	13 (20.75%)
Cold pressure test	48 (80%)	-	12 (20%)

Table 3: Dysfunction In Control And NIDDM Subjects.

Tests	Control (n=30)	NIDDM (n=60)
Valsalva ratio	1.42+0.03	1.23+0.16
E:I ratio	1.30+0.08	1.17+0.12
30:15 beat ratio	1.19+0.05	1.03+0.10
Postural hypotension	12.08+8.72	6.20+2.41
Handgrip test	16.44+3.25	14.12+2.13
Cold pressure test	15.36+4.33	09.12+2.16

REFERENCES:
1. Spallone V, Ziegler D, Freeman R, Bernardi L, Frontoni S, Pop-Busui R et al. Toronto Consensus Panel on Diabetic Neuropathy. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. *Diabetes Metab Res Rev* 2011; 27: 639-653.
2. Vinik AI, Erbas T, Casellini CM. Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. *J Diabetes Investig* 2013; 4: 4-18.
3. Pop-Busui R. What do we know and we do not know about cardiovascular autonomic neuropathy in diabetes. *J Cardiovasc Transl Res* 2012; 5: 463-478.
4. Dimitropoulos G, Tahrani AA, Stevens MJ. Cardiac autonomic neuropathy in patients with diabetes mellitus. World J Diabetes. 2014 Feb 15;5(1):17-39.
5. Vinik AI, Erbas T, Casellini CM. Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. J Diabetes Investig. 2013 Jan;4(1):4-18.
6. Maser R, Lenhard M, DeCherney G. Cardiovascular autonomic neuropathy: the clinical significance of its determination. Endocrinologist. 2000 Jan;10:27-33.
7. Spallone V, Ziegler D, Freeman R, et al.; Toronto Consensus Panel on Diabetic Neuropathy. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. Diabetes Metab Res Rev. 2011 Oct;27(7):639-53.
8. Balcıoglu AS, Müderrisoglu H. Diabetes and cardiac autonomic neuropathy: Clinical manifestations, cardiovascular consequences, diagnosis and treatment. Diabetes Care. 2010 Feb;33(2):434-41.
9. Tandon R, Bajpai, Agarwal et al. Comprehensive study of autonomic nervous system dysfunction in diabetes mellitus. JAPI 1985; 33: 265-268.
10. Lokohtia M, Shah PKD, Jain H, Prihar MK et al. Clinical dysautnomic in diabetes mellitus: a study with seven autonomic reflex function tests. JAPI 1997; 75: 271-274.
11. Sharpey, Schafer Ep, Taylor PJ. Absent circulatory reflexes in diabetic neuritis. Lancet 1960; 1: 559562.