Original article:

Prevalence of cardiac autonomic neuropathy in short and long standing type ii diabetics in western Maharashtra

Chhaya Ahire*, Varsha Sarode **, Kirankumar Jadhav*, Veena Shriram*, Nishi Gaidhani*.**

*Assistant professor, ** Associate Professor, Department of Physiology, B.J.G.M.C Pune , India

*** Associate professor, Department of Surgery, B.J.G.M.C Pune , India

Corresponding author: Dr Chaya Ahire

Date of submission: 12 June 2014 ; Date of publication: 15 September 2014

Abstract:

Introduction: There are currently 60 million people estimated with diabetes mellitus [DM] in India. The number is expected to double by 2040. It has been observed that mortality of diabetic patients with cardiac autonomic neuropathy [CAN] is greater than those without it. So we undertook this study to know prevalence of CAN in diabetics.

Methodology: This is a cross sectional comparative study, which involved 60 randomly selected patients with type II DM [Group I- short duration of 0-5 years (n=30) and group II- long duration of >5 years (n=30)] and 30 control group of healthy subjects. Prevalence of CAN in diabetic patients was evaluated by categorizing patients using various scoring systems such as Ewing's criteria, Bellavere's criteria and AIIMS AFT Lab criteria.

Results and conclusion: High prevalence of CAN in short as well as long standing diabetics suggest that screening for cardiac autonomic function should be done at the moment when diabetes is diagnosed to prevent further complications

Key words: Cardiac autonomic neuropathy, type II DM, Disease duration

Introduction

Autonomic neuropathy is the most common complication of Diabetes, which mainly affects the cardiovascular system, gastrointestinal system and urogenital system. The neuropathic disorder includes manifestations in the somatic and/or autonomic parts of the peripheral nervous system". [1] Diabetic autonomic neuropathy [DAN] can involve both parasympathetic and sympathetic nervous systems, Cardiovascular autonomic neuropathy [CAN] is the earliest form of autonomic dysfunction, which causes abnormalities in heart rate control as well as defects in central and peripheral vascular dynamics. Clinical symptoms of CAN such as resting tachycardia, exercise intolerance, orthostatic hypotension generally do not appear until long after the onset of diabetes. However, subclinical autonomic dysfu-nction can occur within a year of diagnosis in type II diabetes patients and within two years in type I diabetes patients

Type II DM is constituting about 90% of the diabetic population in the Asians. With advancement in the age and duration of diabetes, there is a gradual tendency for the level of blood sugar to rise. It has been observed that mortality of diabetic patients with cardiac autonomic neuropathy is greater than those without it. [2] In view of the immense clinical significance of CAN, it is essential to detect this disorder as early as possible by simplest diagnostic tests. It can be diagnosed by batteries of tests that

show abnormalities of autonomic pathway. Hence the present study was designed with an objective of finding the prevalence of CAN in long and short standing diabetes mellitus.

Material and methods

The study was conducted in the Department of Physiology and Department of Medicine from August 2009 to 2011. The study was approved by the ethical committee of institution. Inclusion criteria of our study was : Controlled type II DM patients between 40 and 60 years, non smokers, non alcoholics and non tobacco chewers with Body Mass Index < 30 kg/m^2. Exclusion criteria : history of cardiovascular diseases including hypertension, subjects with history of thyroid or other endocrine disorders, patient having drug history which affect autonomic functions (β blockers, antipsychotics, anticholinergics), patient with Diabetic ketoacidosis and any other acute complication of DM.

Based upon these criteria, subjects were thoroughly interviewed and clinically examined. Thus a total of 90 subjects were selected for the present study and were divided into three groups as follows –

Group	**Selected subjects / patients**	
Control	30 subjects, non diabetic, age and gender matched	
Study	Group I (30 patients)	0- 5 yrs of type II DM
	Group II (30 patients)	> 5 yrs of type II DM

TESTS:-

A] Tests based on heart rate for assessment of cardiovascular autonomic status

[To test parasympathetic component].-

1] Heart-rate response to deep breathing test: - The subject was in supine position with all ECG leads attached. After breathing normally for 2 minutes, the patient was asked to perform 6 maximum deep breathings in one minute. Continuous ECG record was obtained. E: I ratio was obtained by following formula. [2,3,4]

$$\text{E: I ratio} = \frac{\text{Mean value of longest RR interval during expiration}}{\text{Mean value of shortest RR interval during deep inspiration}}$$

2] Heart-rate response to Valsalva maneuver: - The subject was in sitting position with all ECG leads attached. Each subject performed the valsalva maneuver for 15 seconds by blowing against a closed glottis through a mouthpiece attached to a sphygmomanometer and maintain a pressure of 40 mm Hg for 15 sec. Three trials were performed at intervals of 5 minutes. A continuous ECG was recorded 1 min before the maneuver (resting period), during the maneuver (strain period, 15 sec.) and 1 min subsequent to the strain period. The valsalva ratio was calculated as follows. [2,3,4]

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

$$\text{Valsalva ratio} = \frac{\text{Longest RR interval after the maneuver}}{\text{Shortest RR interval during the maneuver}}$$

3] Immediate Heart-rate response to standing :- Each subject was asked to lie quietly for 3 minutes. He was then asked to stand up and remain motionless. A continuous ECG was recorded and a point was marked on ECG paper to identify the point of standing. The 30:15 ratio was calculated by taking the ratio of the R-R interval at 30th beat and at 15 th beat after standing. [2,3,4]

B] Tests based on blood pressure for assessment of cardiovascular autonomic status [To test sympathetic component]

4] Hand Grip Test (HGT): - It is Blood Pressure Response to Static Exercise. The subject was asked to apply pressure on a handgrip dynamometer [Inco-Ambala] for 1 minute at 30% of maximal voluntary contraction and simultaneously the blood pressure, by using automatic digital machine-[Omron] changes were observed. The difference between the diastolic blood pressure (DBP) just before the release of contraction and before handgrip began, was taken as a measure of the response. [2,3,4]

5] Cold Pressor Test (CPT) :- Resting BP was recorded with the subject sitting comfortably, following which his hand was immersed in cold water and the temperature was maintained at 4-6^{0}C throughout the procedure. BP measurement was made from the other arm at 30-second intervals for a period of 2 minutes. After 2 minutes, the subject was asked to remove his hand. The maximum rise in the diastolic pressure was recorded. [2,3,4]

Table I- Normal, borderline, and abnormal values in above tests

Tests	Normal(score 0)	Borderline(score1)	Abnormal(score2)
Heart-rate (R-R interval) variation during deep breathing. (E:I ratio)	≥ 1.21	1.11-1.20	≤ 1.10
Heart-rate response to Valsalva maneuver (Valsalva ratio)	≥ 1.21	1.11-1.20	≤ 1.10
Immediate heart-rate response to standing (30:15 ratio)	≥ 1.04	1.01-1.03	≤ 1.00
Blood-pressure response to sustained handgrip (increase in diastolic blood pressure)	≥16 mmHg	11-15 mmHg	<10 mmHg
Blood-pressure response to cold pressor test(increase in diastolic blood pressure)	≥16 mmHg	11-15 mmHg	<10 mmHg
Blood-pressure response to standing (fall in systolic blood pressure)	≤10 mmHg	11-29 mmHg	≥30 mmHg

Categorization of subjects for CAN based on different criteria:

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

The cardiovascular tests are classified as tests based on heart rate and tests based on blood pressure. This approach is useful clinically because it reflects the apparent sequence of abnormalities seen in diabetic subjects. Ewing et al. [6,7] ,have advised classification of the degree of autonomic involvement as early, definite or severe rather than as sympathetic and parasympathetic. For this they used

- Deep breathing test (E:I ratio)
- Valsalva Maneuver
- 30:15 ratio
- Handgrip test
- Lying to standing test (orthostatic test)

Categorization as per Ewing's criteria

Category of CAN	Criteria
Normal	All tests normal or one test borderline
Early	One of three heart rate tests abnormal or two borderline
Definite	Two heart rate tests abnormal
Severe	Two heart rate tests abnormal+ one or both BP tests abnormal

Similarly, Bellavere et al [8], have given a scoring to determine the severity of CAN. According to this , score 0 to 2 is assigned for each test as shown in table I and the total score were obtained after addition of below three tests score :-

- Deep breathing test
- Valsalva maneuver
- Lying to standing

Categorization as per Bellavere's criteria

Classification- category	Total Score
No CAN	0-1
Early CAN	2-3
Definite CAN	4-6

AIIMS (All India Institute of Medical Sciences) AFT (Autonomic function Test) Laboratory categorize patients based on parasympathetic and sympathetic component. [9]

The score obtained for parasympathetic component was based on:-

- Deep breathing test
- Valsalva maneuver
- Lying to standing

The score obtained for sympathetic component was based on:-

- Lying to standing test
- Handgrip test
- Cold pressor test.

Based on AIIMS AFT Lab criteria- Scoring for parasympathetic and sympathetic component separately.

Category	Criteria
Normal	All tests normal or one test borderline
Early	One test abnormal or two tests borderline
Definite	Two tests abnormal

Observations and results :

Table II - Demographic profile:

PARAMETERS	CONTROL (n=30)	GROUP-I (<5yrs) (n=30)	GROUP-II (>5yrs) (n=30)
Age (in years)	51.23 ± 6.68	48.43 ± 5.75	52.33 ± 5.28
Sex (M:F)	23:7	21:9	23:7
Systolic BP (mmHg)*	125.0 ± 3.51	132.93 ± 4.86	131.80 ± 6.33
Diastolic BP (mmHg)*	71.46 ± 3.27	82.06 ± 6.54	78.60 ± 7.65
Fasting BSL (mg/dl)*	80.77 ± 16.39	85.90 ± 5.49	91.06 ± 10.40
Postprandial BSL (mg/dl)*	127.76 ± 5.72	128.53 ± 4.92	140.0 ± 27.01
Duration of DM (in years)	_	3.20 ± 1.16	7.83 ± 1.96
BMI (kg / m^2)	23.39 ± 1.05	22.93 ± 1.17	22.77 ± 1.24

Values are expressed in Mean ± SD

-* indicates that though statistically significant difference is seen, values were

Table-III- Categorization of CAN based on Ewing's criteria

No.	Category	Gr-I (n=30)	Gr –II (n=30)
1.	Normal	10% (n= 3)	0
2.	Early	80% (n= 24)	33.33 (n= 10)
3.	Definite	0	23.33% (n= 7)
4.	Severe	0	20% (n= 6)
5.	Patients not classified	10% (n= 3)	23.33% (n= 7)

Table IV - Categorization of CAN based on Bellavere's criteria

No.	Category	Group I (n=30)	Group II(n=30)
1	No CAN	10% (n = 3)	3.33% (n=1)
2	Early CAN	36.66% (n=11)	26.66%(n=8)
3	Definite CAN	53.33% (n = 16)	70% (n= 21)

Table V - Categorization of CAN based on AIIMS AFT Lab criteria

No.	Category	Group I (n=30)		Group II (n=30)	
		Parasymp	**Sympath**	**Parasymp**	**Sympath**
1	Normal	20%(n= 6)	6.66%(n= 2)	3.33% (n=1)	0
2	Early	80%(n=24)	93.33% (n=28)	56.66% (n=17)	76.66%(n=23)
3	Definite	0	0	40% (n=12)	23.33%(n=7)

Table VI - Component of ANS that is affected based on AIIMS AFT Lab criteria

Component	Gr-I (n=30)	Gr-II (n=30)
Pure sympathetic	10% (n= 3)	3.33%(n= 1)
Pure parasympathetic	6.66% (n= 2)	0
Sympathetic + Parasympathetic (Mixed)	83.33% (n= 25)	96.66% (n= 29)

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

DISCUSSION

After applying Ewing's and Bellavere's criteria (table III and IV) results indicate that there is severe autonomic dysfunction in long duration diabetic patients as compared to short duration diabetic patients. The Bellavere's criteria uses the tests that only represent the parasympathetic component while Ewing's criteria uses the tests for parasympathetic as well as sympathetic component . But in Ewing's criteria only sympathetic component used for diagnosis of severe CAN hence 10% in Gr-I and 23.33% in Gr-II patients cannot be classified.

Our data suggest that longer the duration of diabetes , the more likely is the occurrence of hyperglycemic states in spite of controlled diabetes. The positive correlation of duration and CAN has been reported by Alexandra, valensi. [10,11,]According to AIIMS AFT lab criteria [table V, VI] combined abnormality is seen in 83.33% of patients in Gr-I, in the form of early parasympathetic and early sympathetic dysfunction and in 96.66% of patients in Gr-II in which percentage of patients with definite parasympathetic and sympathetic dysfunction increased, indicating that both parasympathetic and sympathetic functions were affected in both the groups. Similar study conducted in tertiary center by AIIMS observed that in diabetes mellitus patients, sympathetic abnormality was more common than parasympathetic component. [9]

According to most researchers, like Ewing, Talman, Bennett, Wheleers and Watkin, cardiac parasympathetic damage occurs early in diabetes mellitus while sympathetic innervations are preserved because of greater susceptibility to axonal degeneration by the longer fibers. Or early parasympathetic involvement may however be more apparent than real because heart rate tests are more sensitive than blood pressure tests and therefore more likely to show abnormalities. Similarly V.S Ganesan et al, L. barkai and L.Madacsy found that incidence of parasympathetic involvement being more common than sympathetic in cardiovascular autonomic dysfunctions. [12,13]

Therefore they concluded that during the course of diabetes, parasympathetic dysfunction may appear earlier than sympathetic damage, as has been suggested elsewhere. Ninković V, Ninković S and Zivojinović D., found that a positive correlation between the values of the parasympathetic score and HbA1c. The same pattern exists regarding the ratio of damage of the sympathetic part of the autonomic nervous system and the value of HbAlc.[14] This indicates that it is not necessary that parasympathetic dysfunction is followed by the development of sympathetic dysfunction, an assumption that is made by Ewing's criteria.

Hence our results show that subclinical autonomic nerve damage occurs more widely in diabetics than was hitherto suspected and is assuming greater importance because of the implications for morbidity and mortality. Findings of our study suggest that screening for cardiac autonomic function should be done at the moment when diabetes is diagnosed to prevent further complications as above mentioned tests are reliable, reproducible, simple, non invasive and quick to carry out. Such early screening can significantly reduce the mortality and morbidity in diabetic patients and thereby decrease the global burden of cardiac autonomic neuropathy arising due to diabetes mellitus.

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

Limitations of the study:

Results would have been more appropriate if sample size could be more and if study design was a prospective study unlike in ours where sample size was small and design was a cross-sectional study

.**Bibliography**

1. American Diabetes Association and American Academy of Neurology: Report and recommendations of the San Antonio Conference on diabetic neuropathy (Consensus Statement). Diabetes. 1988; 37: 1000–1004.

2. Aron I. vinik, Raelene E. Master, Braxton,Roy freeman. Diabetic Autonomic neuropathy. Diabetes Care. 2003 May ;26:1553-79.

3. G.K.Pal. Textbook of Practical Physiology. 2nd ed. Orient Longman Pvt. Ltd. 2005:296-303.

4. A.K.Jain. Manual of Practical Physiology. Arya Publications ; 2008:279-284.

5. Low PA, Walsh JC, Huang CY, McLeod JG. The sympathetic nervous system in diabetic neuropathy: a clinical and pathological study. Brain. 1975;98:341–56.

6. Ewing DJ, Campbell IW, Clarke BF. Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. Ann Intern Med. 1980;92:308-1.

7. Campbell, Ewing, Clark. Tests of cardiovascular function in diabetic autonomic neuropathy. Horm Metabo Rec. 1979;6:4-7.

8. Bellavere F, Basello G, Fedele P, Cardone C, Ferri M. Diagnosis and management of diabetic autonomic neuropathy. Br. Med. J. 1983;287:61.

9. Ekta khandelwal, Ashok kumar jaryal, Kishore kumar Deepak. Pattern and prevalence of cardiovascular autonomic neuropathy in diabetics visiting a tertiary care referral center in India. Indian J Physiol Pharmacol 2011; 55(2):119-127.

10. Alexandra Diana Comanescu. Subclinical diagnosis of cardiovascular autonomic neuropathy in type 2 diabetes:Prevalance,severity,correlations with time, metabolic and vascular factors. Romanian journal of neurology. 2010; 9 (1):57-62. 11. P. Valensi , J. Pariès, J. R Attali. Cardiac autonomic neuropathy in diabetic patients: influence of diabetes duration, obesity, and microangiopathic complications—the french multicenter study. 1990; (9): 49-53.

12. V.S. Ganesan, S. Venkataraman, A. Sundaram, R.S. Hariharan, R. Madhavan, N. Manjula and V. Seshiah . Autonomic Neuropathy And Diabetic Foot Syndrome. Diabetes[Internet]. 1988 Jan; 12: 89-95. Available from: http://www.diabetes.org/1988/jan/htmArticle

13. L Barkai, L Madacsy. Cardiovascular autonomic dysfunction in diabetes mellitus. Archives of Disease in Childhood. 1995;73: 515-18.

14. Ninković V, Ninković S, Zivojinović D. Cardiovascular autonomous dysfunction in diabetics: the influence of disease duration, glycoregulation degree and diabetes type. Srp Arh Celok Lek. 2008 Sep-Oct;136(9-10): 488-93.