

Assessments of Predominance of Cardiac Autonomic Neuropathy in Iraqi Diabetic Subjects

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ABSTRACTS:

BACKGROUND:

Autonomic nervous system is well known to be affected by endocrine diseases and metabolic disorders, hyperglycemia plays an integral role in this aspect which might alter both sympathetic and parasympathetic components.

OBJECTIVE:

The study was designed to assess the cardiac autonomic neuropathy in Iraqi diabetic subjects and to determine which division will be predominant (sympathetic or parasympathetic).

Settings

Department of Physiology in the Medical College of AL Mustansyriah University and the Section of Neurophysiology in Al Yarmouk Teaching Hospital.

PATIENTS AND METHODS:

Sixty subjects with Type 1 diabetes mellitus and sixty with Type 2 diabetes mellitus were enrolled in this study and their studied parameters were compared to sixty healthy individuals free from glucose intolerance assured by normal Oral Glucose Tolerance Test (OGTT) were regarded as a control group. Cardiovascular autonomic tests for all subjects (healthy and diabetics) were done by using Ewing's battery reflex tests.

RESULTS:

The results revealed the presence of significant difference between diabetic groups (type 1 & type 2) and control group regarding autonomic reflex tests including blood pressure response to standing and hand grip test ($p < 0.05$) in type 1 DM and blood pressure response to standing ($p < 0.01$) in type 2 DM. In this study 68.33% of diabetic subjects showed abnormal response to one or more of the performed tests. Also sympathetic involvement was found to be more common; (38.33%) for postural hypotension and (46.66%) for diastolic response to sustained hand grip testing while the parasympathetic division showed (32.75%) for valsalva maneuver and (31.66%) for beat to beat heart rate variation testing and (18.33%) for heart rate response to standing.

CONCLUSION:

Diabetes mellitus affects cardiac autonomic system adversely with predominance to sympathetic division more than the parasympathetic component and this affection is aided by the duration of diabetes. So better glycemic control can delay the occurrence of cardiac complications associated with diabetes mellitus and in turn may improve life expectancy in diabetic subjects.

KEY WORDS :diabetes mellitus. cardiovascular autonomic neuropathy. ewing's battery reflex

INTRODUCTION:

Autonomic neuropathy is an important cause of diabetic morbidity, and is related to the age of subject and duration of disease⁽¹⁾, also it was strongly associated with retinopathy⁽²⁾.

Diabetic autonomic neuropathy can develop in subjects with type 1 or type 2 diabetes. Although autonomic neuropathy may occur at any stage of diabetes^(3,4) usually it develops in subjects who have had the disease for 20 years or more with poor glycemic control. In autonomic disease, the

sympathetic, parasympathetic, and enteric nerves are affected. Myelinated and unmyelinated nerve damage is found. Diabetic autonomic neuropathy may lead to hypoglycemic unawareness⁽⁴⁾.

The risk of cardiovascular events is at least two to four times higher in patients with diabetes. Cardiovascular neuropathy is a result of damage to vagal and sympathetic nerves⁽⁵⁾. The incidence of cardiac autonomic neuropathy (CAN) appears to be around 15% in type 1 and 20% in type 2 diabetic subjects⁽⁶⁾. Clinical findings may include exercise intolerance, persistent sinus tachycardia, no variation in heart rate during activities, and bradycardia.⁽⁶⁾

The tests used in this projects to assess the cardiac autonomic neuropathy are those which proposed by

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Ewing et al⁽⁷⁾ as these tests are simple, non invasive and easy reproducible as shown in table 1 Which reveals the normal and abnormal values for each studied test.

Table 1: Ewing's battery tests for cardiovascular autonomic reflex tests (normal and abnormal values).

Tests	Method	Normal value	Border value	abnormal
1- Heart rate response to Valsalva maneuver.	Valsalva ratio	>1.21	1.11-1.20	<1.10
2- Heart-rate variation during deep breathing. (by ECG).	Maximum-minimum of heart rate.	>15 beat/min.	11-14 beat/min.	<10 beat/min
3-Immediate heart-rate response to standing.(by ECG)	R-R interval ratio of 30 th beat :15 th beat	>1.04	1.01-1.03	<1.00
4- Blood pressure response to standing.	Measure blood pressure in supine and then in stand	<10 mmHg.	11-29 mmHg.	>30(20) mmHg.
5- Blood pressure response to sustained handgrip. (2 min.)	Measure diastolic blood pressure after 2 min using of hand grip	>16 mmHg	11-15 mmHg	<10 mmHg

SUBJECTS AND METHODS:

Three groups were included in the present study; healthy individuals as the control group, Type 1 and Type 2 diabetic subjects. Cardiac autonomic function tests were carried out for all.

Healthy control group:

Control group consists of sixty healthy individuals (30 males and 30 females); their mean age was 36.6 ± 2.10 years (Mean ±SEM). All subjects were healthy with no history of systemic illness (diabetes, hypertension or heart problem) or family history of neurological disorders, and all showed normal oral glucose tolerance test. **Diabetic subjects:**

The diabetic subjects enrolled in this study were divided into two groups:-

a- Type 1 diabetic subjects comprise of sixty subjects (28 male & 32 female) and their mean age was 34.87±2.03 years with duration of diabetes 9.23±1.40 years.

b- Type 2 diabetic subjects consist of sixty subjects (38 males and 22 females), their mean age was 39.5±1.12 years with duration of diabetes 6.04±0.99 years.

METHODS:

1- Heart rate response to deep breathing (i.e., beat-to-beat heart rate variation, R-R variation)

The patient lies quietly and breathes deeply at a rate of six breaths per minute (a rate that produces maximum variation in heart rate) while ECG records the difference between the maximum and minimum heart rates.

2- Heart rate response to standing

This test evaluates the cardiovascular response elicited by a change from a horizontal to a vertical position. The patient is connected to an electrocardiogram (ECG) monitor while lying down and then stands to a full upright position.

ECG tracings are used to determine the 30:15 ratio, calculated as the ratio of the longest R-R interval (found at about beat 30) to the shortest R-R interval (found at about beat 15).

3- Valsalva maneuver

In the standard Valsalva maneuver, the subject lies in supine, connected to an ECG monitor, forcibly exhales for 15 seconds against a fixed resistance (40 mmHg) with a close glottis. A sudden transient increase in intrathoracic and intra-abdominal pressures, with a consequent hemodynamic response will result.

The Valsalva ratio is determined from the ECG tracings by calculating the ratio of the longest R-R interval after the maneuver (reflecting the bradycardic response to blood pressure overshoot) to the shortest R-R interval during or shortly after the maneuver (reflecting tachycardia as a result of strain).⁽⁷⁾

4- Systolic blood pressure response to standing

Blood pressure normally changes only slightly on standing from a sitting or supine position. In normal individuals, the systolic blood pressure falls by <10 mmHg in 30 seconds. In diabetic subjects with autonomic neuropathy, baroreflex compensation is impaired. A response is considered abnormal when the diastolic blood pressure decreases more than 10 mmHg or the systolic blood pressure falls by 30 mmHg within 2 min after standing (8, 9 and 10). (Table 1)

5- Diastolic blood pressure response to sustained handgrip

In this test, sustained muscle contraction as measured by a handgrip dynamometer causes a rise in systolic and diastolic blood pressure and heart rate. The dynamometer is first squeezed to isometric maximum, and then held at 30% of the maximum for 5 minutes. The normal response is a

rise of diastolic blood pressure >16 mmHg, whereas a response of <10 mmHg is considered abnormal⁽¹⁰⁾ Subjects with Diabetic Autonomic Neuropathy(DAN)are more likely to exhibit only a small diastolic blood pressure rise.⁽¹⁰⁾

RESULTS:

The cardiac autonomic tests in control subjects in both sexes revealed no differences in all studied parameters, so the data were pooled together and dealt with as single group as shown in (table 2).

Table 2: Cardiac autonomic tests in control subjects in both sexes .

Cardiac autonomic tests	Female n=30	Male n=30	P- value
Valsalva ratio	1.44±0.04	1.51±0.06	(NS)
Heart rate change with breathing	19.29±1.49	18.44±2.12	(NS)
Immediate heart-rate response to standing (30:15 ratio)	1.21±0.02	1.19±0.03	(NS)
Blood pressure change on standing(mmHg)	8.57±0.72	6.2±1.51	(NS)
Diastolic blood pressure change with hand grip test (mmHg)	16.80±1.32	20.86±1.51	(NS)

Table 3 :Comparison of cardiac autonomic reflex tests between control and diabetic subjects.

	Control (C) n=30 mean ± SEM	Type 1 n=30 mean ± SEM	Type 2 n=30 mean ± SEM	P values Control vs. type 1	P values Control vs. type 2	P values Type1 vs. type 2
Valsalva ratio	1.48±0.037	1.39±0.049	1.37±0.054	(NS)	(NS)	(NS)
Heart rate change with breathing	18.87±1.24	18.13±1.60 3	18.70±1.25	(NS)	(NS)	(NS)
Immediate heart-rate response to standing (30:15 ratio)	1.20±0.022	1.17±0.037	1.16±0.04	(NS)	(NS)	(NS)
Blood pressure change on standing(mmHg) normally <10	7.39±0.61	10.7±1.48	13±1.82	0.042	0.004	(NS)
Diastolic blood pressure change with Hand grip test (mmHg) normally>16	18.83±1.059	15.48±0.97 4	16.70±1.21	0.0235	(NS)	(NS)

In cardiac autonomic reflex tests, there were only two significant differences between control subjects and type1 DM as shown in table (3) ; in the blood pressure changes on standing (P =0.042) and diastolic pressure change with hand grip test (P = 0.0235).

While the statistical difference between control and type 2 showed only one significant difference detected in blood pressure change on standing (P = 0.004).

There were no significant differences in all cardiac autonomic reflex tests between type 1 and type 2 DM so both groups were gathered and delt with as an unique group.

Cardiac autonomic reflex tests in Iraqi diabetic subjects.

The results of cardiac autonomic reflex tests are shown in table (4). It has been found that 46.7% of subjects had abnormal diastolic blood pressure response to sustained hand grip. Furthermore, 38.3% of diabetics had abnormality in blood pressure response to standing. The results also indicated that 32.8% of diabetic subjects had abnormal valsalva ratio.

Also 31.7% of diabetics had abnormal heart rate variation during deep breathing and 18.3% of them had abnormal 30:15 ratio.

Table 4: Cardiac autonomic reflex tests in diabetic subjects.

tests	Normal Response(%)	Abnormal Response	
		Border line (%)	Definite (%)
Valsalva manoeuvre*	39 (67.24%)	10 (17.24%)	9 (15.51%)
H.R. Variation during deep breathing	41 (68.33%)	8 (13.33%)	11 (18.33%)
30:15 ratio	49 (81.66%)	3 (5%)	8 (13.33%)
B.P. response to standing	37 (61.66%)	20 (33.33%)	3 (5%)
B.p. response to sustained hand grip	32 (53.33%)	14 (23.33%)	14 (23.33%)

* Two subjects were not able to perform valsalva test.

DISCUSSION:

For all parameters of cardiovascular autonomic reflex tests done : the type 1 diabetic subjects showed a decrease in the effect of hyperglycemia on autonomic nervous system only two significant difference observed which were the change in blood pressure change on standing ($p=0.042$) and change in diastolic blood pressure on hand grip test ($p=0.024$) Such results was in a harmony with Ewing et al.⁽⁸⁾, and Vinik et al.^(9,10,13).

In spite of all groups in this study were normotensive, Type 2 diabetic subjects in this study showed a significant high mean systolic and diastolic blood pressure as compared with controls, but type 1 diabetic subjects showed non significant higher systolic and diastolic blood pressure when compared to control group. This finding enforces previous studies reported by Sowers⁽¹⁴⁾ that confirm the preceding of cardiovascular disease to occurrence of the metabolic syndrome in type 2 diabetes mellitus.

Again all parameters of cardiovascular autonomic reflex tests in type 2 diabetic subjects showed a decrement values when compared to control group which explain the effect of diabetes mellitus on autonomic nervous system reaching a significant difference in blood pressure change on standing when compared to control group ($p=0.004$).

Such results were in harmony with Ewing et al.⁽⁸⁾, and Vinik et al.^(9,10,13).

It was found that sometimes one of the parameters of the autonomic nervous system tests may be abnormal, but the other tests turn out normal. This is because some tests as heart rate variability tests are more sensitive to earlier autonomic nervous system dysfunction than others. This is also due to the fact that test results are based on a combination of activities within the body, which are influenced differently in each subject.

Nearly same conclusion was reached to by Ewing⁽¹⁶⁾ in his statement that although one might speculate that parasympathetic damage occurs earlier than sympathetic damage, this may not always be true. The increased frequency of abnormalities detected via the tests of the parasympathetic system may merely be a reflection of the test (e.g., sensitivity) and not of the natural history of nerve fiber damage. Thus, it may be better to describe the natural history of autonomic dysfunction as developing from early to more severe involvement rather than to anticipate a sequence of parasympathetic to sympathetic damage.

In this study 68.33% of diabetic subjects showed abnormal response to one or more of the performed tests. This is in total agreement with the studies of Page and Lloyd-Mostyn^(17,18) which have put the incidence of autonomic neuropathy in diabetics to be about 70%, while Ganesan et al.⁽¹⁹⁾ showed 79.16% and Kubba et al. (20) showed incidence of 64%.

In this study sympathetic involvement was found to be more common; (38.33%) for postural hypotension and (46.66%) for diastolic response to sustained hand grip testing while parasympathetic involvement include; (32.75%) for valsalva maneuver and (31.66%) for beat to beat heart rate variation testing and (18.33%) for heart rate response to standing. These figures were in disagreement with Ganesan and Kubba (19,21) who showed that parasympathetic involvement is more than sympathetic. Such disagreement between the two findings may be attributed to the effect of hypertension and smoking which were ruled out in the current study; as the control of heart rate through the parasympathetic nervous system has been reported to be reduced in essential

hypertension together with an enhanced sympathetic and circulatory response to provocative tests. In diabetic subjects, hypertension was associated with a higher frequency of abnormal heart rate tests, i.e., valsalva maneuver⁽²²⁾, whereas the commonly increased sympathetic tone observed in essential hypertension was not preserved in the hypertensive diabetic subjects. Since variability in heart rate plays an important role in controlling blood pressure by minimizing pressure oscillations and since this effect is mediated by vagal pathway, the relationship between cardiac autonomic impairments and hypertension might express a complex dysfunction in autonomic control of cardiovascular system as mentioned by Menzinger⁽²³⁾.

Also smoking acutely increases sympathetic activity and catecholamine levels, which is the main mechanism for increased cardiovascular risk in smokers. Moreover, smoking acutely produces acute and transient decrease in vagal activity. Chronic heavy smoking causes long-term reduction in parasympathetic control⁽²⁴⁾ with increased resting heart rate and decreased heart rate variability, but in mild to moderate smokers it does not strongly affect autonomic function⁽²³⁾.

Results showed that there were abnormality in two or more tests of cardiovascular autonomic function as 36.6% in type 2 vs. 33.3% in type 1 diabetic subjects. This finding was in harmony with a study done by Ziegler⁽²⁵⁾ who showed cardiovascular autonomic neuropathy occurs more commonly in patients with type 2 diabetes mellitus than type 1. This may be attributed to delay in diagnosis of metabolic abnormality and high Body Mass Index(BMI) in type 2 diabetic subjects.

CONCLUSION:

The results of this study ensures the hazardous effect of hyperglycemia on the autonomic nervous system with special focusing on cardiac autonomic nervous division, also this hazardous effect is aided by prolongation in the duration of diabetes mellitus.

REFERENCES:

1. Godbole SA, Deepak KK, Kochark, :Correlates of severe autonomic neuropathy. *Diabetologia*;1997, 40 (suppl. 1) 561 (abstract).
2. Krolewski AS, Barzilay J, Warram J II., : Risk of early onset proliferative retinopathy in IDDM is closely related to cardiovascular autonomic neuropathy. *Diabetes*;1992, 41:430-437.
3. Novella SP, Inzucchi SE, Goldstein JM: The frequency of undiagnosed diabetes and impaired glucose tolerance in patients with idiopathic sensory neuropathy. *Muscle Nerve*;2001;24:1229-31.
4. Singleton JR, Smith AG, Bromberg MB: Increased prevalence of impaired glucose tolerance in patients with painful sensory neuropathy. *Diabetes Care*;2001;24:1448-53.
5. American Diabetes Association: Consensus development conference on the diagnosis of coronary heart disease in people with diabetes; 10-11 February 1998, Miami, Florida. *Diabetes Care*;1998, 21:1551-9.
6. Zielger D: Cardiovascular autonomic neuropathy: Clinical manifestation and measurement. *Diabetes Rev*;1998, 7:342-57.
7. Ewing DJ, Martyn CN, Young RJ, Clarke BF: The value of cardiovascular autonomic function tests: 10 years experience in diabetes. *Diabetes Care*;1985;8:491-98.
8. Ewing DJ, Campbell IW, Clark BF: A ssesment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. *Ann Intern Med*;1980;92:308-11.
9. Vinik AI, Holland MT, Le Beau JM, Liuzzi FJ, Stansberry KB, Colen LB: Diabetic neuropathies. *Diabetes Care*;1992;15:1926-75.
10. Vinik AI, Suwanwalaikorn S: Autonomic neuropathy. In *Current Therapy of Diabetes Mellitus*. De Fronzo RM, Ed. St. Louis, MO, Yearbook;1997: 165-76.
11. Ewing DJ: Analysis of heart rate variability and other non invasive tests with special references to diabetes mellitus. In *Autonomic failure*. 3rd ed. Bannister R, Mathias CJ, Eds. Oxford Medical;1992: 312-33.
12. Ziegler D, Laux G, Dannehl K, Spuler M, Muhlen H, Mayer P, Gries FA: Assessment of cardiovascular r autonomic function: age-related normal ranges and reproducibility of spectral analysis, vector analysis, and standard tests of heart rate variation and blood pressure responses. *Diabetic Med*;1992;9:166-175.
13. Vinik A, Erbas T, Pfeifer M, Feldman E, Stevens M, Russell J: Diabetic autonomic neuropathy,. In *The Diabetes Mellitus Manual: A Primary Care Companion to Ellenberg and Rifkin's 6th Edition*. Inzucchi SE, Ed. New York, McGraw Hill; 2004:351.
14. Sowers R: Insulin resistance and hypertension. *Mol. Cell. Endocrinol.* 1990;74:C87-C89.

15. Edelson GW, Sowers JR.: Insulin resistance in hypertension: a focused review. *Am. J. Med. Sci.*1993;306:345-47.
16. Ewing DJ: Diabetic autonomic neuropathy and the heart. *Diabetes Res Clin Prac* 1996;30 (Suppl.) S31-S36.
17. Page MM, Watkins PJ: The heart in diabetic autonomic neuropathy and cardiomyopathy. *Clin. Endocrin. Metab.*1977; 6: 377-88.
18. Lloyd-Mostyn RH and Watkins PJ.: Defective innervation of the heart in diabetic autonomic neuropathy. *Br. J.*1975;3:15-7.
19. Ganesan VS, Venkataraman S, Sundaram A, Hariharan RS, Madhavan R, Manjula N, Seshiah V.: Autonomic neuropathy and diabetic foot syndrome;1988: 89-96.
20. Kubba S, Agarwal SK, Prakash A, Puri V, Babbar R, Anuradha S. : Effect of losartan on albuminuria, peripheral and autonomic neuropathy in normotensive microalbuminuric type 2 diabetics. *Neurology India*;. 2003;51: 355-58.
21. Tuch PS, Gill GV, Huddle KR: Autonomic neuropathy in African diabetic patients. *Postgraduate Medical Journal*;1994; 70:188-91.
22. Ricordi L, Rossi M, Marti G, Finardi G, Fratino P, Bernardi L: Hypertension in diabetes: an additional factor determining autonomic neuropathy. *Diabetes Nutr Metab*;1989;2:269-75.
23. Menzinger Guido: Diagnosis of cardiovascular autonomic neuropathy in diabetes. (Current State and Perspectives of Diabetes Research: Chronic Complications). *Diabetes*;1997: 9/1.
24. Hayano J, Yamada M, Sakakibara Y, Fujinami T, Yokoyama Y, Watanabe Y, Takata K: Short- and long-term effects of cigarette smoking on heart rate variability. *Am J Cardiol*;1990;65:84-88.
25. Ziegler D, Gries FA, Muhlen H, Rathmann W, Spuler M, Lessmann F: Prevalence and clinical correlates of cardiovascular autonomic and peripheral diabetic neuropathy in patients attending diabetes center. The DiaCAN Multicenter Study Group. *Diabet Metab*; 1993;19:143-51.