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AUTONOMIC DYSFUNCTION AND PERIPHERAL VASODILATORY RESPONSE IN DIABETES

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Abstract: Twenty three diabetes mellitus patients were investigated for peripheral vasodilatory response in relation to degree of autonomic dysfunction. The non-insulin dependent diabetes mellitus (NIDDM) patients had significant degree of autonomic dysfunction. Based on standard scoring system for evaluating autonomic dysfunction, diabetics were divided into 'borderline' (n = 12) and 'severe' (n = 11) diabetic autonomic neuropathy (DAN) groups. The severe DAN patients showed significantly lower pressor response when compared to borderline DAN patients. Severe DAN was also associated with significant peripheral vascular dysfunction. The severe DAN patients largely had no clinical manifestation of peripheral vascular dysfunction. Thus, at subclinical level patients with significant autonomic dysfunction do exhibit peripheral vascular dysfunction.

Key words: autonomic dysfunction, diabetes mellitus, ankle-brachial index, peripheral vascular dysfunction.

INTRODUCTION

Autonomic functions (1) and peripheral vascular status (2) have been reported to be abnormal in non-insulin dependent diabetes mellitus (NIDDM). These two changes alongwith sensory-motor neuropathy are important in the genesis of typical 'diabetic foot'. Vasoconstriction response to slow breathing and body cooling shows significant reduction (3) in NIDDM patients. In the present study we assessed the status of peripheral vascular dysfunction (exercise induced vasodilatory response, measured by Ankle/Brachial index) in a group of patients with varying degree of involvement of autonomic functions in NIDDM patients.

METHODS

Twenty three diabetics were studied (Table I). None of the patients gave history of alcoholism, dietary deficiency and history of intake of drug known to affect peripheral and/or autonomic nervous system. Twenty five (19M, 6F; mean age ± SD: 26 ± 8 years) normal subjects acted as control. All patients and controls underwent a battery of five standard tests for assessment of their autonomic function (4) viz, deep breathing, Valsalva manoeuvre, isometric hand grip test, cold pressor test and head-up tilt (HUT).

After 5 min rest of sitting in chair, subject performed deep breathing (breathing at 6/min) and Valsalva manoeuvre (40 mm Hg rise in pressure during forceful expiration for 15 sec). After 10 min rest in supine position, head-up tilt test (70^0 tilt in 15 sec) was performed. Continuous ECG and respiration were

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monitored. With deep breathing E:I (R-R interval during Expiration versus Inspiration) ratio and difference in heart rate (Inspiration-Expiration) were calculated. With Valsalva manoeuvre Valsalva ratio and difference in heart rate (phase II – phase IV) were calculated. For head-up tilt 30:15 ratio and drop in systolic pressure at 5th min of tilt were measured. All tests were performed using standard procedures. Data are presented as mean ±SD. The group means were compared and scores were computed.

For non-invasive vascular assessment a continuous wave doppler ultrasound system (Vasilab IV, Kodys) was used with a 8 MHz probe. A pneumatic cuff with an inflatable bladder of 20% more width than limb diameter was used to record the resting and post-exercise pressures. The resting and post-exercise pressures were taken over the brachial artery in the arm and the posterior tibial artery at ankle in the leg on either side. The ankle brachial index (ABI) is the ratio of ankle and Brachial pressures. The ABI for right and left side were calculated separately. After recording the systolic arterial pressures over the brachial and posterior tibial arteries during rest in supine position, the patients were asked to perform exercise using a step test. The test consisted of climbing up the down on improvised step (platform) of 12 cm height at a rate of 30 steps per min for 2 min. This exercise is equivalent to exercising on a treadmill at 1.7-2.0 mph on 10% gradient for 3 min; in terms of oxygen requirement, 17.5 ml/kg/min. The test was terminated if any patient developed claudication, shortness of breath or fatigue. After completion of exercise, patients were returned to supine position, then arm and ankle systolic pressures were estimated after 1 min (post exercise) on both the sides. A cut-off level of 0.8 was taken to be an indicator of peripheral vascular disease (< 2 SD of normals) (5). Fifteen of 23 patients were evaluated for ABI. Two of the patients could not perform exercise. The NIDDM patients were divided into two subgroups depending on severity of involvement of autonomic function. To determine severity of autonomic involvement, in diabetic patients, a standard method (6) was used and each patient's autonomic functions were scored depending on its deviations from the normal score. Each of the parameters (E:I, Valsalva and 30:15 ratios; rise in DBP in hand grip test and change in DBP during head-up tilt) were scored as 0 (when > mean –1SD of normal); 1 (between mean –25D and mean –1SD of normal) or 2 (value < mean –2SD of normal). This score was summed up to give total score. This score was used to classify the diabetic patients into subgroups (7): severe diabetic autonomic neuropathy (score > 5), borderline diabetic autonomic neuropathy (score 2 to 5) and normal (score < 2) groups.

RESULTS

Table I gives clinical and laboratory profile of 23 diabetic patients. Diabetic patients had significantly reduced E:I ratio, Valsalva ratio, 30:15 ratio and showed less rise in diastolic pressure at 4th min of isometric exercise (Fig. 1). The diabetics showed maximum fall in diastolic pressure (HUT) with a value 16.64 ± 4.65 (mean ± SD) which was higher than normals ($P < 0.05$). Clinically the two subgroups

TABLE I: Clinical and laboratory characteristics of the 23 diabetic patients.

Parameters	*Range*	*Mean ± SD*
Age (years)	28 – 75	51 ± 11
Sex (M : F)	18 : 5	
Duration (years)	1 – 24	10.91 ± 6.65
FBS (mg/dl)	90 – 212	144 ± 36.0
GHb (%)	4.7 – 12.4	8.23 ± 2.09
Treatment :		
Insulin/OHA	11/12	

FBS : Fasting blood sugar; GHb : Glycated hemoglobin; OHA : Oral hypoglycaemic agent.

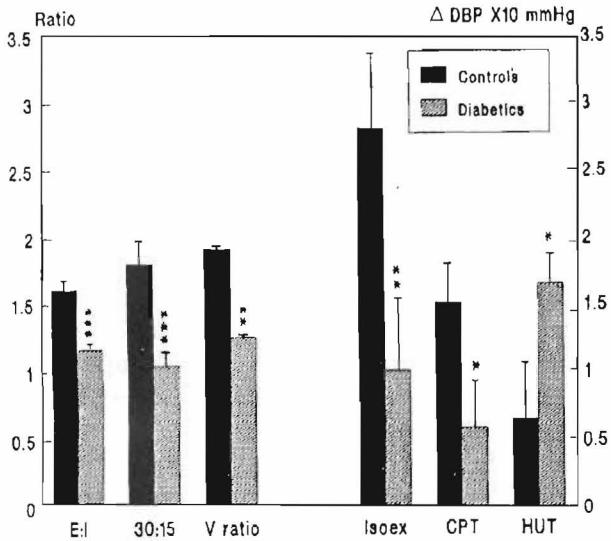

Fig. 1: Comparison between control subject (n=25) and diabetics (n=23) for autonomic function tests. DBP, diastolic blood pressure; E:I, Expiration to inspiration ratio during 6/min deep breathing; V ratio, Valsalva Ratio; Isoex, percentage rise in diastolic pressure during hand grip exercise; CPT rise in diastolic pressure during cold pressor test; HUT, maximum fall in diastolic pressure during 70° head-up tilt. Standard deviation is shown above each bar.
Significance *P < 0.05, **P < 0.001, ***P < 0.001

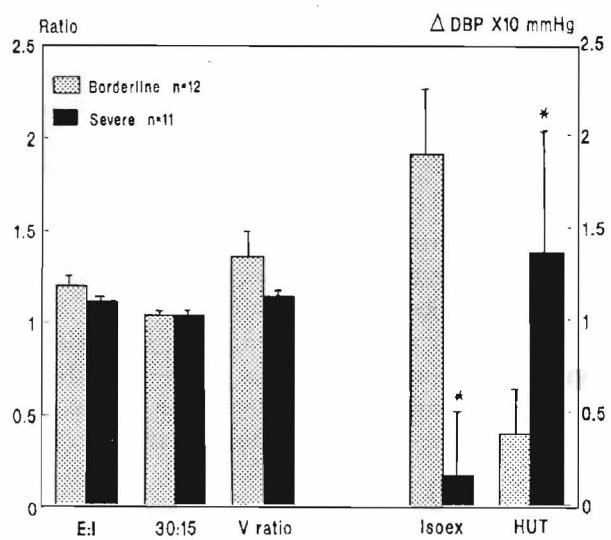

Fig. 2: Comparison of borderline and severe diabetics Abbreviation are same as for Fig. 1.

of diabetic neuropathy (based on autonomic scoring) were compared. Except that the severe DAN had higher age ($P < 0.05$) they were not statistically different for duration of illness, post-glycaemic control (as indicated by FBS and GHb respectively), and frequency of one or more autonomic symptoms (Table II).

The blood pressure responses to isometric hand grip and postural changes (head-up tilt) were significantly worse in severe DAN than

TABLE II: Clinical Features of Diabetic Autonomic Neuropathy

Features	*Borderline n=12*	*Severe n=11*
Age (years)	45 ± 10	55 ± 10
Duration (years)	9.6 ± 7.4	12 ± 5.9
OHA/insulin (%)	66.6/33.47	36.4/63.6
FBS (mg/dl)	148 ± 31	140 ± 41
GHb (%)	9.21 ± 1.37	7.24 ± 2.8
Symptoms of peripheral neuropathy	7/12(58.3%)	11/11(100%)
Impotence	8/10	8/8
Bladder symptoms	7/12	5/11
Sweating disturbances	5/12	5/11
Esophageal gastric symptoms	1/12	3/11
Intestinal symptoms	8/12	7/11
Postural symptoms	4/12	2/11

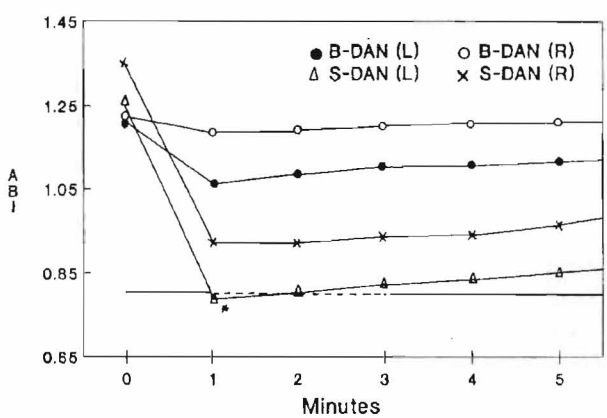

Fig. 3: Resting (at 0 min) and post-exercise (1 to 5 min) ankle brachial pressure index (ABI) for patients with borderline (B-DAN, n=8) and severe diabetic autonomic neuropathy (S-DAN, n=5). R, right side ABI; L, left side ABI.

borderline DAN ($P < 0.01$) (Fig.2). The ankle-brachial index was found significantly lower at 1 min post-exercise ($P < 0.05$) in severe DAN as compared to borderline DAN (Left = 0.78 vs 1.05; Right = 0.93 vs 1.19, $P < 0.05$) (Fig.3). Interestingly, the resting ABI was not significantly different in the two subgroups.

DISCUSSION

This study confirms the loss of varying degree of autonomic function in long standing diabetes (1). Further evaluation of peripheral vascular function suggests that it is a late onset phenomenon and correlates well with severity of diabetic autonomic neuropathy (DAN).

Among the clinical correlates of severity of DAN, only age was found to be statistically high in severe DAN cases. This is in concurrence with earlier studies. In an Indian study of 72 diabetics, patients with single or multiple clinical features of autonomic neuropathy had significantly higher mean age than patients without any clinical features of autonomic neuropathy (8).

Age dependent E:I ratio showed lower value in severe DAN patients who are a decade older than borderline DAN patients. A large Chinese study also documented that heart rate variation during single deep breath and three consecutive deep breaths declined significantly with age (9). Another large study on insulin dependent diabetics showed that average heart rate variability decline over 10–15 years was 1.02 beats per annum which is faster decline than non-diabetics in whom heart rate variability fell at rate of 0.30 to 0.46 beats per annum between ages of 30–50 years (10). This suggests that diabetes mellitus accelerates the normal age related decline in autonomic function.

The duration of diabetes was more in patients with severe DAN when compared to borderline ones, although this did not attain statistical significance (Table II). Inspite of this, atleast two tests showed significant difference between severe DAN and borderline DAN; these were rise in DBP during sustained hand grip and fall in DBP during head-up tilt (level of significance for both was $P < 0.005$). This suggests early parasympathetic involvement (both groups affected) and late sympathetic involvement as seen in severe DAN. Alternatively, these findings may also suggest that parasympathetic parameters do not aggravate progressively beyond a point in DAN. However, we are less definite in putting this statement forward because such conclusion should be drawn from a prospective study rather than from a cross-sectional study.

Significantly reduced one min post exercise ABI indicates peripheral vascular disease in severe DAN as compared to borderline cases (Fig. 3). In this study only two patients each from borderline DAN and severe DAN groups had history of foot ulceration. This suggests that degree of severity of DAN is correlated with peripheral vascular disease (PVD) (as measured by ABI) even before its end point namely ulcer is reached. This deduction may be criticised on the grounds that the study compares more central visceral cardiovascular autonomic functions (reflexive in nature) with PVD and presumes that the former reflects a parallel degree of peripheral autonomic nerve function. While sensitive tests for peripheral autonomic function like sudomotor function and microvascular reflex are available, the existing evidence clearly suggests that peripheral sudomotor function in the lower limbs and cardiovascular reflex test do, in fact, correlate well (12).

The observation of ABI at rest and post-exercise suggest that it is only functional reserve which is depleted in DAN as confirmed by study

of microvascular flow studies (2). Clinically also this finding is confirmed by gradual claudication and foot ulcer. In conclusion, our data suggests existence of correlation between autonomic dysfunction and peripheral vascular dysfunction at subclinical level.

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