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Study of Clinical Evaluation of Autonomic Dysfunction in Type 2 DM

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Abstract: *Diabetic autonomic neuropathy (DAN) is usually less recognizable than diabetic sensory motor peripheral neuropathy early in the course of Type 2 diabetes mellitus. Subclinical autonomic nerve damage occurs more widely in patients with diabetes mellitus than was hitherto suspected and is assuming greater importance because of the implications for morbidity and mortality. By the time symptoms have developed, autonomic damage in majority of the organs is irreversible and carries a poor prognosis. There is a need to detect autonomic neuropathy at an early stage.*

In view of this we studied on 100 patients of Type 2 diabetes mellitus who attended Diabetic Clinic (Every Friday) in Government General Hospital, Vijayawada. With the simple non invasive tests of cardiovascular reflex function, objective assessment of autonomic neuropathy was made. Ewing, et al introduced a test battery for studying autonomic damage in diabetic patients. This battery has been widely accepted as a means to classify autonomic neuropathy in terms of its severity. Detecting autonomic dysfunction using cardiovascular autonomic function tests might help to improve the quality of life and expectancy of affected patient.

Key words: *Atherosclerosis, Autonomic neuropathy, Autonomic function tests, Diabetes and Lipid profile.*

I. Introduction

Diabetic autonomic neuropathy (DAN) is a serious and common complication of Diabetes. [1] Despite its relationship to an increased risk of cardiovascular mortality and its association with multiple symptoms and impairments, the significance of DAN has not been fully appreciated. With regard to autonomic neuropathy cardiovascular autonomic neuropathy most common complication in type2 Diabetes mellitus. [1, 2] This is easily overlooked and characterized by damage to the autonomic nerve fibres that innervate the heart and blood vessels resulting in abnormalities of heart rate control and vascular dynamics. [3]

Around 75% of people with Diabetes die from cardiovascular disease such as myocardial infarction and cerebral stroke.[4] Silent ischemia is significantly more frequent in patient with diabetic autonomic neuropathy than without (38% Vs 5%).[5] Therefore early subclinical detection of cardiovascular autonomic neuropathy for risk stratification and preventing serious consequences is of prime importance. The world wide prevalence of Diabetes Mellitus has risen over past two decades. It is estimated that >552 million individuals will have diabetes by the year 2030. Estimated 366million cases in 2011.[6]

In 2010 the estimated global prevalence of diabetes was 6.6% of the adult population and is projected to reach 9.9% by 2030. More than 90% of cases of diabetes are type 2 diabetes mellitus. In India alone, the prevalence of diabetes is expected to increase from 30 million in 2000 to 80 million in 2030. Diabetes mellitus is the leading cause of blindness in working-age adults in the United States; diabetic retinopathy accounts for 12,000-24,000 newly blind persons every year. [7]

Diabetes mellitus is the leading cause of end-stage renal disease (ESRD), accounting for 44% of new cases, according to the Centres for Disease Control and Prevention (CDC).[8] In 2005, 46,739 people in the United States and Puerto Rico began renal replacement therapy, and 178,689 people with diabetes were on dialysis or had received a kidney transplant.[9] Diabetes mellitus is the leading cause of non traumatic lower limb amputations in the United States, with a 15- to 40-fold increase in risk over that of the non diabetic population.[9]

Autonomic Neuropathy is one of the complications of diabetes, develops slowly over the years. Diabetes Mellitus related autonomic neuropathy can involve multiple systems, including the cardiovascular, gastrointestinal, genitourinary and metabolic systems. Diabetic autonomic neuropathy impairs the ability to conduct activities of daily living, lowers quality of life, and increases the risk of sudden death. It also accounts for a large portion of the cost of care [1] Intensive glycemic control is critical in preventing the onset and

slowing the progression of DAN. The diabetic complications and control trial (DCCT) showed that intensive glycaemic control reduced the prevalence of autonomic dysfunction by 53%. [10] Around 75% of people with diabetes die from cardiovascular disease such as myocardial infarction and cerebral stroke. 25% to 50% die within 5 to 10 years of diagnosis. [4] Leading cause of death in diabetic patients with either symptomatic or asymptomatic autonomic neuropathy was heart disease. [2] Autonomic neuropathy is also an independent risk factor for cerebral stroke.

Cardiovascular autonomic neuropathy occurs in about 17% of patients with Type 1 diabetes and 22% of those with type 2 DM. Silent myocardial ischemia shown to be associated with cardiac autonomic neuropathy in T2DM, thus amplifying the risk of arrhythmia and cardiac adverse events. [11] Cardiovascular autonomic neuropathy causes abnormalities of heart rate control and vascular dynamics. [3] It has been linked to postural hypotension, Exercise intolerance, enhanced intraoperative cardiovascular morbidity and increased incidence of asymptomatic ischemia myocardial infarction and decreased likelihood of survival after myocardial infarction. [1] Clinical symptoms of autonomic neuropathy generally do not appear early, until long duration after the onset of diabetes. Subclinical autonomic dysfunction can, however, occur within a year of diagnosing type 2 diabetes patients and within two years in type 1diabetes patients. [12] By the time the symptoms have developed, autonomic damage in majority of the organs is irreversible and carries a poor prognosis (Ewing and Clarke, 1982). So there is a need to detect autonomic neuropathy at an early stage.

With the introduction of simple non invasive tests of autonomic function it is possible to study autonomic neuropathy. Ewing et al introduced a test battery for studying autonomic damage. [13] Autonomic dysfunction can affect daily activities [eg, exercise] of individuals with diabetes and may invoke potentially life-threatening outcomes and also associated with increased intra operative cardiovascular mortality. [14] The patient's history and physical examinations are ineffective for early detection of autonomic nerve dysfunction, therefore the use of simple non invasive tests are recommended. The present study was under taken to identify clinically autonomic neuropathy in type2 diabetes mellitus patients.

II. Materials And Methods

This study was conducted on 100 patients of Type 2 diabetes mellitus who attended Diabetic Clinic (Every Friday) in Government General Hospital, Vijayawada in the age groups 20-75 years of both sexes. This study was approved by the institutional ethics committee. Written informed consent was taken from the patients in local language. This was an observational, retrospective and cross sectional study.

2.1 Inclusion Criteria:

All patients of Type 2 Diabetes Mellitus of both sexes who attended Diabetic Clinic in the Government General Hospital, Vijayawada were included.

2.2. Exclusion Criteria: subjects who were alcoholics, CCF, COPD, Ischemic heart disease, arrhythmia, chronic liver disease and with pregnancy were excluded**.**

2.3. Careful history was taken regarding symptoms suggestive of autonomic dysfunction. Detailed neurological examination was done in all the patients.

2.4. The Blood Investigations: complete blood count, blood urea, S.Creatinine, S.cholesterol, and S. Bilirubin, urine analysis, ECG, FBS, PPBS, 24 hours urinary proteins and Chest X-ray were done.

2.5. Fundoscopy was done in all cases and the changes of diabetic retinopathy were noted.

2.6.24 Hr urinary Protein was estimated. Diabetic nephropathy is diagnosed if urinary albumin excretion is more than 30 mg/day.

2.7. Corrected QT interval (QTc interval) was calculated from the ECG.

2.8. QT interval/√RR interval. The normal range of QTc interval is from 0.35 sec to 0.43 secs.

2.9. 1.BMI is calculated from the weight and the height of the subject using the formula : Weight in kgs / (height in meter)².

2.9.2. Waist –hip ratio: WHR is the ratio of body circumference measured midway between the iliac crest and the lowest rib, to that at the level of the greater trochanters.

A ratio of >0.95 in males and >0.80 in females is considered as abnormal.

2.10. Cardiovascular Autonomic Reflex Function Tests (Ewing's battery of five tests) these included-

2.10.1. Heart rate response to valsalva manoeuvre (valsalva ratio**):** The subjects were asked to blow into a mouth piece attached to an aneroid pressure at a pressure of 40 mm Hg and to hold it for 15 seconds. The ratio of the longest RR interval shortly after the manoeuvre (within 20 beats) to the shortest RR interval during the manoeuvre was then measured. The mean of three successive readings was taken.

2.10.2. Heart rate response to deep breathing**:** The subject was asked to breathe deeply and evenly at 6 cycles / min (6 sec inspirations and 4 sec expiration) the ventilator cycle with the maximum difference between maximal and minimal heart rate was chosen for analysis and is expressed as E-I difference. And also E/I ratio were measured as RR interval expiration/ RR Interval inspiration.

2.10.3. Heart rate response to immediate standing (30:15 ratios)**:** The subject was asked to lie quietly on a couch and then asked to stand up unaided as quickly as possible .the ratio of the longest RR interval around the 30th beat after standing up to the shortest RR interval around the 15th beat was calculated.
2.10.4. Blood pressure response to standing**:** The blood pressure was measured while the subject was lying down, and again 1 minute after standing up. The fall in systolic pressure is taken as the measure of postural blood pressure change.
2.10.5. Blood pressure response to sustained hand grip: Hand grip was maintained at 30% of the maximal voluntary contraction for up to a maximum of 5 minutes using a conventional sphygmomanometer and the blood pressure just before release of handgrip and before starting the test is measured.
Based on the above tests (Ewing's criteria) clinical dysautonomia was classified according to the severity of damage into five groups. [13]

III. Results

This study was done for a period of one year at Government General Hospital and Siddhartha medical college Vijayawada, Andhra Pradesh, India. Of the 100 total number of subjects 60 (60%) were males and 40 (40%) were females. The age of the patients ranged from 24 – 72 years, and had a mean of 42 ±8 yrs. The median age of the subjects was 40years.The mean duration of type 2 diabetes in this study was 4 years. 39(39%) of our subjects had diabetes for more than 4 years and 61(61%) of our subjects with duration of diabetes less than 4 years.
Distribution of various symptoms of Autonomic Neuropathy in Type 2 DM was shown in table no 1.

Table No 1: Distribution of Symptoms of Autonomic Neuropathy in Type 2 DM

Symptoms	No of subjects	Percentage
Postural hypotension	60	60
Bladder disturbances	53	53
Upper GIT symptoms	20	20
Diarrhoea	28	28
Constipation	24	24
Sweating changes	30	30
Sleep disturbances	23	23
Sexual dysfunction	33	33
Impotence (males only)	20	20
Irritation of eyes	58	58

GIT= Gastrointestinal tract.

The symptoms suggestive of autonomic neuropathy were present in 90 subjects (90%), 10 subjects (10%) were asymptomatic. The most common symptom was postural hypotension present in 60 subjects (60%) followed by irritation of eyes (58%). Among the 60 males sexual dysfunction was the most common symptom, which was present in 55%, next common was bladder disturbances seen in 50% of the subjects. Among subjects with positive sensory symptoms (i.e. in 51)39 had clinical autonomic dysfunction .In subjects who had negative sensory symptoms (47 in no) 16 subjects had clinical evidence of autonomic dysfunction. 51 out of 100 subjects who had diabetes for more than 4years had symptomatic diabetic poly neuropathy however it was not statistically significant.

The body mass index of our subjects (BMI) ranged from 19- 34 , with mean 26. Among subjects with BMI >30, 86% of subjects had clinical dysautonomia which was clinically significant (p value 0.04). WHR of the study population ranged from 0.68-1.30, with mean score 0.97. Among the male group (60 in no) WHR was high (i.e. >0.95) in 31 subjects. In these 31 subjects, 23 (74 %) had clinical autonomic neuropathy. No of females with high WHR (>0.80) were 37, among these 29 (78 %) had clinical autonomic neuropathy. Neurological findings in our subjects were as follows- The most common sign elicited was absent ankle jerk, which was seen 23 subjects (23%) next common sign was decreased pain &temp sensation 51 out of 100 subjects who had diabetes for more than 4years had symptomatic diabetic polyneuropathy however it was not statistically significant. All subjects were using oral hypoglycemic drugs and 20 patients were on combination of insulin and oral hypoglycemic drugs 60 subjects were prescribed anti hypertensive drugs. Lipid lowering agents like satins were given to 60% of the diabetics & anti platelets were given to 70% of the subjects.

Clinical autonomic function tests: A non invasive Ewing's battery of five cardiovascular Autonomic function tests was done in all hundred subjects. The values of these tests were classified according to Ewing's criteria as normal, borderline & abnormal and are shown in the table no.2

Table No 2: Ewing's Cardiovascular Autonomic Function tests.

Ewing's Test	No .of Subjects		
	Normal	Borderline	Abnormal
1) E: I Ratio	63	27	10
2) Valsalva Ratio	50	39	11
3)30: 15 Ratio	48	24	28
4)BP To Standing	34	55	11
5)BP To Sustained Hand Grip	22	46	32

BP= Blood Pressure.

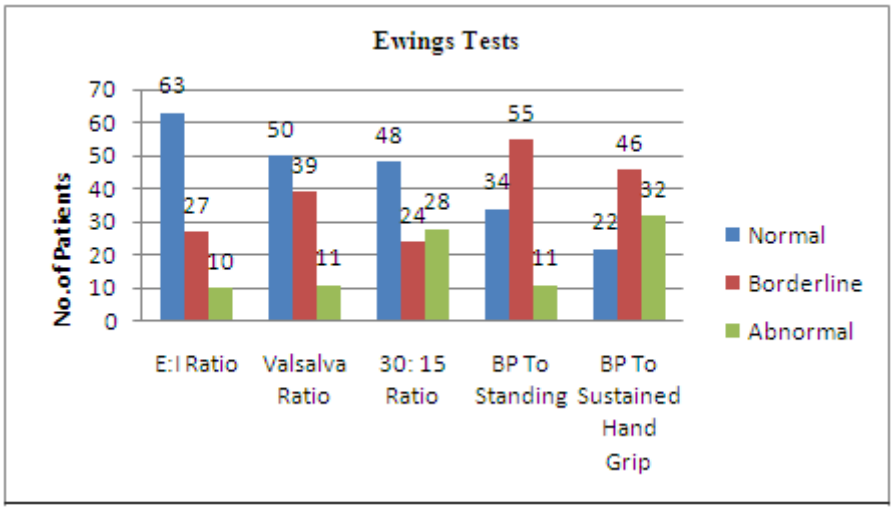

Figure 1: Ewing's test with the five cardiovascular autonomic function tests.

The abnormal responses were most frequently found for blood pressure response to a sustained hand grip test (32%).The results of these five tests were categorized as normal, early pattern, definite, severe, atypical form Of 100 subjects, 42 had early pattern of autonomic dysfunction, 26 had normal pattern, 22 had atypical form, 5 had definite pattern & 5 had severe pattern.

The base line characteristics of our study group after classification according to diabetic autonomic neuropathy, subjects with DAN,subjects without DAN were shown in table.3

Table No 3: Classification of study group with diabetic autonomic neuropathy

	WITH OUT DAN	WITH DAN
No of subjects	26	74
Age (yrs)	40±8.9	42±8.9
Sex(M/F)	17/9	43/31
Duration of diabetes(yrs)	3.8±2.6	6.6±2.5*
BMI (kg/m2)	25.3±2.8	26.3±3.1
WHR	0.92±0.133	0.98±0.134
HB(g/dl)	11.7±1.5	11.3±1.5
FBS(mg/dl)	133±35	145±35
PPBS	203±43	218±45
% of subjects with↑LDL	6	30*
S.creatinine(mg/dl)	1.2±0.53	1.4±0.5
24 hr urinary protein gm/day	198±80	232±79*

Values expressed as mean± standard deviation, *indicates p value significant compared to subjects without DAN= Diabetic autonomic neuropathy, BMI= Body mass index, WHR=Waist hip ratio, HB= Haemoglobin, FBS= Fasting blood sugar and LDL=low dense lipoproteins.

The subjects with cardiovascular autonomic neuropathy significantly older than those without autonomic neuropathy, but the mean duration of diabetes in the subjects did not differ significantly. Subjects with autonomic neuropathy also had significant higher LDL cholesterol.The clinical dysautonomia was seen in 43 male subjects & in 31 female subjects, but incidence of dysautonomia was higher (77%) among females, compared with males which was 72%. The Percentage of subjects with autonomic neuropathy higher in elder (>60) age group (100 %) than in <40 yrs(78%) and in 41 – 60 yrs (62%) . In subjects with duration of diabetes > 4 yrs (39 in no), 30 had clinical dysautonomia (77%) which was clinically significant (p value <0.05)

Diabetic retinopathy changes were observed on fundoscopy in 28 subjects, among these 21 had clinical dysautonomia (75%). Diabetic nephropathy was found in 43 subjects, among these 36 had clinical dysautonomia (83%). QTc interval was prolonged in 34 subjects, in these 30 had dysautonomia.

IV. Discussion

Autonomic neuropathy is a common complication of diabetes which is easily overlooked. Cardiovascular autonomic neuropathy is associated with high rates of mortality & morbidity. [1, 2] So approaches to manage cardiovascular autonomic neuropathy could reduce mortality and morbidity of diabetic patients. The prevalence of autonomic neuropathy, based on autonomic function testing i.e. Ewing's battery of five tests, was reported to be between 7.7 and 90%. [1]

In our study out of 100 (60 males, 40 females) 74 (74%) were defined as having autonomic neuropathy. The prevalence of autonomic neuropathy in our study was very similar to the reported prevalence (73% in type 2 diabetes <0.01) a population based study by Philip A, Low eta. [15] Dyck et al [16] reported a neuropathy prevalence of 59% in type2 diabetes in the Rochester, Minnesota, population. Valensi et al., reported prevalence of cardio vascular autonomic neuropathy in diabetes was 51%. [17] In the present study subjects were defined as having autonomic neuropathy based on Ewing's battery of five tests, these tests are better in detecting the autonomic involvement than a single test done alone which has been advocated by Burgos, Ewing, Camurgos, Ewing, Campbell Etal.[18,19]

In our study mean age of subjects with autonomic neuropathy was 42±8.9 and without autonomic neuropathy 40±8.9 which was not statistically significant (P = 0.8) however the % of subjects with autonomic neuropathy higher in elder (>60yrs)age group(100 %) than in <40 yrs(78%) and in 41 – 60 yrs (62%) .These observations were in consistent with other studies that have shown that autonomic neuropathy correlates strongly with age. [20, 21] The duration of diabetes in subjects with autonomic neuropathy was 6.6±2.5 which was statistically significant (P=0.04).Studies in the past have shown an increase in the incidence of clinical dysautonomia with increasing duration of diabetes mellitus. [22] In our study we did not observed that prevalence of autonomic neuropathy differed significantly with age & gender, but the duration of diabetes is significant than in patients without autonomic neuropathy.

The patients with autonomic neuropathy had significantly higher LDL cholesterol. We found that the male patients tend to have higher LDL cholesterol than the female patients, but this was not statistically significant. In our study the most common symptom was postural hypotension present in 60 subjects followed by irritation of eyes. Among males sexual dysfunction was most common symptom (55%) which was in concordance with previous studies. [23] In a study by Ewing DJ 95% males were impotent. [24] Bladder disturbances was present in 53% which was consistent with study by Caramori et al. [25] The upper and lower gastrointestinal symptoms which include gastroparesis as well as constipation and diarrhoea was found in 36% of subjects which correlate with other studies. [26, 27, 28] Clinically 36 out of 100 subjects who had diabetes for more than 4years had symptomatic diabetic polyneuropathy however it was not statistically significant p value 0.06. The most common sign was absent ankle jerk. In our study 74 out of 100 had clinical dysautonomia ie 74% which was in concordance with study by clement et al. [29] in a study conducted by Lakhotia M et al [30], dysautonomia was found in 64% of subjects with diabetes mellitus. The abnormal responses were most frequently found for blood pressure response to a sustained hand grip test (32%), which was consistently with study by moon et al. [31] Postural blood pressure test yielded a few abnormal responses (11%), as similar to study by Meyer et al (14%) . [32]Heart rate response to the deep breathing test yielded the fewest abnormal responses (10%).The study conducted by Barthwal et al had detected heart rate response to deep breathing and valsalva ratio to be the most sensitive while postural hypotension to be the least sensitive index. [33]

In our study 5 subjects (5%) had definite autonomic neuropathy, but a study by valensi et al reported 26.3% had definite cardiovascular autonomic neuropathy. [17] 42% had early cardiovascular autonomic neuropathy. These observations were consistent with other studies. [34, 35] In the present study diabetic retinopathy changes were observed on fundoscopy in 28 subjects, among these 21 had clinical dysautonomia (75%) i.e 2/3 rd subjects with diabetic retinopathy had clinical dysautonomia which was in concordance with a study by Ziegler D etal. [36] In our study diabetic nephropathy was found in 43 subjects, among these 36 had clinical dysautonomia (83%) which was significant. Previous studies also have demonstrated a significant relationship between autonomic neuropathy and diabetic nephropathy. [37, 38] QTc interval was prolonged in 30 subjects out of 74 subjects with clinical dysautonomia (40%), which is less sensitive. Barthwal et al found that QTc interval prolonged correlate with autonomic dysfunction. Several authors have reported that QTc intervals in patients with diabetic autonomic impairment are longer. [33]

V. Conclusion

Prevalence of autonomic neuropathy in type 2 diabetes mellitus was high and correlates with the longer duration of diabetes. Severity of clinical dysautonomia increases with age. The most common symptom was

postural hypotension followed by irritation of eyes. Among males sexual dysfunction was most common symptom. Ewing's clinical autonomic function tests were more sensitive in detecting autonomic dysfunction Among these clinical tests heart rate response to valsalva appeared to be more sensitive than blood pressure response to standing. There is significant relationship between autonomic neuropathy and diabetic nephropathy in our study. Therefore we conclude that cardiac autonomic neuropathy may be considered as one of the risk factor for development of diabetic nephropathy. The incidence of diabetic autonomic neuropathy increases as the complications of diabetes increases. However diabetic retinopathy was least sensitive. QTc interval was least sensitive measure of autonomic dysfunction.

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