

## Original Research Article

# A Study of autonomic nervous system dysfunction among patient with diabetes mellitus: a cross sectional study

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## ABSTRACT

**Background:** Neuropathy is a common complication of diabetes mellitus and it may affect both the peripheral nerves and autonomic nervous system. Its prevalence ranges from 1% to 90%. The present study is therefore designed to investigate autonomic nervous system involvement in diabetes mellitus by using simple bedside tests and to study its association with other diabetic angiopathies.

**Methods:** 100 patients of diabetes mellitus were selected in the study. In Autonomic function tests for evaluating parasympathetic damage E: I ratio, 30:75 ratio and Valsalva ratio test was performed. Sympathetic damage was diagnosed by Blood pressure response to standing test and Blood pressure response to sustained handgrip test.

**Results:** Abnormal E:I ratio was noticed in only 24 patients. The 30:15 ratio was found to be abnormal in 38 patients while the Valsalva Ratio was abnormal in 34 patients. Postural hypotension was observed in only 8% patients. The sustained hand grip test was abnormal in 10 patients. The prevalence of cardiac autonomic neuropathy was 58%. The association between the presence of autonomic neuropathy and peripheral neuropathy was statistically significant. However, the association between autonomic neuropathy and retinopathy and nephropathy was not statistically significant.

**Conclusions:** The overall prevalence of autonomic neuropathy in diabetes mellitus was 58%. There was parasympathetic preponderance over sympathetic nervous system in the involvement of diabetic autonomic neuropathy. There was statistically significant association of diabetic autonomic neuropathy with peripheral neuropathy as compared to retinopathy and nephropathy.

**Keywords:** Autonomic Nervous System, Diabetes Mellitus, Neuropathy, Parasympathetic damage

## INTRODUCTION

Diabetes mellitus is an ancient disease and dates back to centuries before Christ. Charaka and Sushruta of ancient India (600 to 400 B.C.) were aware of many of the currently known facts of the disease and named it "Madhumeha" (rain of honey) as they recognised the sweetness of urine.<sup>1</sup> In India and worldwide prevalence of diabetes mellitus show the dramatic increase in recent years. Near about 40.9 million patients of diabetes

mellitus currently present in India and this number is expected to rise to about 69.9 million by the year 2025.<sup>2</sup> This high burden is likely associated with complications.<sup>3</sup> The nervous system is so frequently involved in diabetes mellitus that neuropathy has been included in the triad of pathological conditions characteristics of this disease retinopathy, nephropathy and neuropathy.<sup>4</sup>

Neuropathy is a common complication of diabetes mellitus, and it may affect both the peripheral nerves and

autonomic nervous system. Diabetes is leading cause of autonomic neuropathy. It's prevalence ranges from 1% to 90%, depending on the diagnostic method, on characteristics of patient cohort and the type of diabetes studied.<sup>5</sup> Although autonomic neuropathy is often subclinical, it is associated with an increased risk for other diabetes complications and mortality.<sup>6</sup> The earliest symptoms related to neuropathy in diabetes are traceable to the writings of John Rollo, the disorder of sweating were presented in papers of Pavy.<sup>7</sup>

Although damage to autonomic nerves involves almost all parts of 'the body, the effect is most obvious in cardiovascular system. Cardiovascular reflex damage is assumed to reflect autonomic nervous system damage elsewhere.<sup>8</sup> The present study is therefore designed to investigate autonomic nervous system involvement in diabetes mellitus by using simple bedside tests and to study its association with other diabetic angiopathies.

## METHODS

The present study was conducted in the department of medicine of SRTR Government medical college, Ambajogai. The present study was carried out on 100 patients of diabetes mellitus attending the outpatient department and patients admitted in medicine wards, during the period of December 2014 to November 2016.

The patient selection was based on the below mentioned inclusion and exclusion criteria.

### Inclusion criteria

- Patients of diabetes mellitus within the age group of 13 to 70 years.
- Patients willing to participate in study.

### Exclusion criteria

- Associated diseases in which autonomic nervous system is affected like, Tabes dorsalis and leprosy etc.
- Patients receiving drugs that are known to interfere with cardiac or respiratory function such as beta-blockers, sympathomimetic drugs, antihypertensives like alpha methyl dopa, diuretics etc.
- Patients with comorbid conditions like ischemic heart disease, rheumatic heart disease, arrhythmia and cardiac failure.
- Patients who cannot cooperate for various tests and physically handicapped patients and those unable to stand up quickly and maintain an erect posture.

By using the above-mentioned inclusion and exclusion criteria total 100 cases of diabetes were enrolled in the present study. Careful evaluation of history and detailed clinical examination was carried out among all the selected patients. Efforts were made specially to find out

symptoms suggestive of autonomic nervous system involvement. After thorough clinical examination, all these patients were subjected for various investigations. Newly detected patients as well as known patients of diabetes mellitus were included in the present study. In all patients diagnosis of diabetes mellitus was made by criteria given American diabetics association 2014.<sup>9,10</sup>

Necessary laboratory investigations were performed in all the patients. Fundus examination and 12 lead ECG was done in all cases. Special investigations like X-ray chest, CSF examination, etc. were done wherever necessary. Peripheral Neuropathy, retinopathy and nephropathy was diagnosed by using standard procedures.

### Autonomic function tests

The following tests of the autonomic nervous system were performed in all patients. The tests were explained to the patients before being actually carried out.

#### Tests reflecting parasympathetic damage

- Heart rate variation during deep breathing (E: I ratio): The subject was made to lie quietly and to breathe deeply at 6 breaths/min. During breathing instantaneous heart rate monitoring was performed electrocardiographically. The expiration: inspiration (E:I ratio) was calculated-as the longest R-R interval during expiration to the mean of shortest R-R interval during inspiration.
- Immediate heart rate response to standing (30:75 ratio): The test is simple to use and requires only a standard electrocardiograph and ability of patients to stand-up a continuous ECG recording and measurement of the R-R interval at beat 15 and 30 after standing to give 30:15 ratio.
- Valsalva ratio: The patients lay comfortably and resting ECG was recorded for 15 seconds. Later the patient was asked to blow into a mouth piece connected to a manometer so as to keep the pressure up to 40 mmHg and to maintain it for 15 seconds while a continuous ECG recording was done. After 30 seconds ECG was monitored again for 15 sec. The Valsalva ratio was calculated as longest R-R interval after release to shortest R-R interval during manoeuvre.

#### Tests for sympathetic damage

- Blood pressure response to standing: When patients stand, 2 min after standing decline in systolic blood pressure by more than 20 mmHg and by more than 10mmHg for diastolic blood pressure is considered abnormal.
- Blood pressure response to sustained handgrip: The patient gripped the inflated cuff with dominant arms three times. Highest of three readings was called maximum voluntary contraction. Subject was instructed to maintain handgrip steadily at 30% of

maximum contraction for as long as possible to a maximum of 4-5 minutes. Blood pressure was measured on non-exercising arm at rest and at the end of grip. The change in blood pressure was recorded as difference between resting reading and after test.

The results were then categorized into one of the 4 groups<sup>11</sup>

- Normal
- Early parasympathetic disturbance- One of the three tests of parasympathetic function abnormal
- Definite parasympathetic disturbance- With 2 of the three tests of parasympathetic function abnormal
- Combined parasympathetic and sympathetic disturbance- When in addition to abnormal parasympathetic disturbance one or both sympathetic tests abnormal.

The collected data was entered using microsoft excel (2007). Statistical analysis was done using SPSS version 10 and was presented with appropriate table and graphs.

## RESULTS

The present study was carried out in 100 cases of diabetes mellitus to investigate autonomic nervous system involvement in diabetes mellitus by using simple bedside tests and to study its association with other diabetic angiopathies.

**Table 1: Distribution of diabetic patients with various characteristics.**

Variable	Number of patients
Age group	13-20
	21-30
	31-40
	41-50
	51-60
	>60
Sex	Male
	Female
Duration of diabetes	0-2
	>2-4
	>4-6
	>6-8
	>8
Complications of diabetes mellitus	Peripheral neuropathy
	Retinopathy
	Nephropathy

It was observed that majority of the patients were in each the age group of 21-30 years and 41-50 years of age group. Out of the total 100 patients studied 70 patients

were male diabetics and 30 patients were female diabetics.

The male to female ratio was 2.3:1. It was noticed that majority of patients (62%) had diabetes mellitus of less than 2 years' duration. Long standing diabetes mellitus of more than 5 years' duration was noted in only 22% patients. The duration varied from 1 month to 10 years. Peripheral neuropathy, retinopathy and nephropathy was observed in 58%, 56% and 8% of patients respectively (Table 1).

Abnormal E:I ratio (beat-to-beat heart rate variation) was noticed in only 24 patients. The 30:15 ratio (heart rate response to standing) was found to be abnormal in 38 patients while the Valsalva ratio was abnormal in 34 patients. Postural hypotension was observed in only (8%) patients whereas. The sustained hand grip test was abnormal in 10 patients (Table 2).

**Table 2: Distribution of patients according to cardiac autonomic neuropathy.**

Test	Cases
E:I ratio	Normal ( $\geq 1.10$ )
	Abnormal ( $< 1.10$ )
30:15 ratio	Normal ( $\geq 1.04$ )
	Abnormal ( $< 1.04$ )
Valsalva ratio	Normal ( $\geq 1.21$ )
	Abnormal ( $< 1.21$ )
Postural hypotension test (systolic BP in mm of Hg)	Normal ( $\leq 20$ )
	Abnormal ( $> 20$ )
Sustained handgrip test	Normal ( $\geq 16$ )
	Abnormal ( $< 16$ )

**Table 3: Incidence of autonomic neuropathy in diabetes patients.**

Incidence of autonomic neuropathy in diabetes patients	Number of patients
Normal	42
Autonomic neuropathy	Early parasympathetic disturbance
	Definite parasympathetic disturbance
	Combined parasympathetic and sympathetic disturbance

The diagnosis of cardiac autonomic neuropathy in diabetes mellitus was done on the basis of criteria discussed under methodology and it was observed that 58% patients were suffering from cardiac autonomic neuropathy. Thus, the prevalence of cardiac autonomic neuropathy was 58% in the present study (Table 3). The association between the presence of autonomic neuropathy and peripheral neuropathy was statistically significant. However, the association between autonomic neuropathy and retinopathy and nephropathy was not statistically significant (Table 4).

**Table 4: Association of autonomic neuropathy with other diabetic angiopathies.**

Diabetic angiopathies		Autonomic neuropathy		P-value
		Present	Absent	
Neuropathy	Present	42	16	$\chi^2=11.778$ , df=1, p=0.00059935*
	Absent	16	26	
Retinopathy	Present	34	22	$\chi^2=0.385$ , df=1, p=0.53493939
	Absent	24	20	
Nephropathy	Present	6	2	$\chi^2=1.032$ , df=1, p=0.30968939
	Absent	52	40	

## DISCUSSION

The present study was conducted among the 100 patients with diabetes mellitus reporting to the study institute during the period of December 2014 to November 2016. The study was conducted with the aim investigate autonomic nervous system involvement in diabetes mellitus by using simple bedside tests and to study its association with other diabetic angiopathies.

The mean age of the study patients was 40.1 years with the range from 12 years to 70 years. Majority of the patients were in the age group of 21-30 years and 41-50 years (20% each group). There were 70 males and 30 females with a male to female ratio of 2.3:1. It was noticed that the majority of the patients (62%) had diabetes of less than 2 years' duration. Long standing diabetes mellitus of more than 5 years' duration was noted in only 22% patients. The duration varied from 1-10 years. The findings were comparable with findings observed by George and Ravindran.<sup>12</sup>

The incidence of peripheral neuropathy was seen in 58% patients. Retinopathy was seen in 56% patients. Nephropathy was noted in only 8% patients. Kudrimoti et al reported peripheral neuropathy in 62.5% patients, retinopathy in 31.4% patients and nephropathy in 15.7% and peripheral vascular disease in 4.3% patients.<sup>13</sup> However, Patel and Shrivastava reported a high incidence of nephropathy 62.35% and the retinopathy was seen in 24.36% patients.<sup>14</sup> In the present study, the incidence of nephropathy was found to be less the probably because the patients with advanced diabetic renal disease (uraemia) were excluded from the study.

In the present study, E:I ratio was noticed to be abnormal in 24 patients (24%). Twenty two out of 24 patients with abnormal E:I ratio had abnormality of other tests of cardiac autonomic function as well. Isolated abnormal E:I ratio was only seen in 2 patients. The findings were comparable with findings reported by Kudrimoti et al where abnormal E:I ratio in 22.9% of patients.<sup>13</sup> Patnaik et al, reported abnormal response in 85.71% which was much higher as compared to the present study.<sup>15</sup> Smiths et al and Pfeifer et al also confirmed that the heart rate

variation during deep breathing is a sensitive index of autonomic dysfunction.<sup>16,17</sup>

The 30:15 ratio (heart rate response to standing) was found to be abnormal in 38 patients. The findings were comparable with the findings reported by reported by Sharma et al (38%), John L et al (46.6%) and Kudrimoti et al (45.3%).<sup>13,18,19</sup> Ewing et al reported the incidence of abnormal 30:15 ratio to be 60%.<sup>20</sup>

Valsalva ratio was the third test utilised in the present study to test integrity of autonomic nervous system. Valsalva ratio was found to be abnormal in 34% patients. Gupta et al, reported abnormal Valsalva ratio in 36.72% patients.<sup>21</sup> Sharma et al and Patnaik et al reported abnormal Valsalva ratio in 38% and 40% patients respectively.<sup>15,18</sup> Levin et al reported higher incidence of 62% of abnormality of Valsalva ratio.<sup>22</sup>

In the present study, postural hypotension was observed in only 8 patients (8%). Gupta et al and Sharma et al reported an incidence of postural hypotension to be 5.7% and 6% respectively.<sup>18,21</sup> John L et al observed postural hypotension in 12% patients and Kudrimoti et al in 17.14% patients and remarked that postural hypotension is a sensitive test of sympathetic dysfunction.<sup>13,19</sup> Hasking et al found postural hypotension to be a late feature and reflects sympathetic involvement.<sup>23</sup>

Sustained hand grip test abnormality was found to be in 10 patients. All patients with positive test had parasympathetic neuropathy also. Ewing et al reported abnormal response to sustained handgrip in 26.22% diabetics.<sup>20</sup> Sharma et al had abnormal handgrip test in 10% patients.<sup>18</sup> The present study findings correlated with findings of Sharma et al.<sup>18</sup>

In the present study out of the total 100 patients of diabetes mellitus, autonomic neuropathy was noticed in 58% of patients. Only parasympathetic involvement was seen in 48% patients, while combined parasympathetic and sympathetic neuropathy was observed in only 10% of patients. Thus 10% patients had total cardiac denervation. No patient with isolated sympathetic abnormality was observed. Thus, the parasympathetic involvement was much more common as compared to sympathetic



involvement. Wide ranges of autonomic neuropathy are quoted by various workers. Das et al has quoted a range of incidence of 20 to 84% of cardiac autonomic neuropathy.<sup>24</sup> Rao et al has quoted a range of prevalence of autonomic neuropathy from 7% in those without peripheral neuropathy to 80% in those with peripheral neuropathy.<sup>25</sup>

Ewing et al reported parasympathetic dysfunction in 55.73% patients and sympathetic dysfunction was seen in 26.33% patients.<sup>20</sup> Gupta and Pandit found an incidence of 66.3% studied in 47 patients with proven diabetes.<sup>11</sup> The findings of the present study correlated well with the studies of Ewing et al and Gupta and Pandit.<sup>11,20</sup> Patnaik et al reported a very high incidence of abnormality (80%).<sup>15</sup> Many workers have reported a lower incidence. John L et al observed an incidence of 40% in patients with diabetes mellitus, whereas Kudrimoti et al<sup>1</sup> reported 34.28% incidence.<sup>13,19</sup> Thus the study confirms that the parasympathetic neuropathy is much more common than sympathetic neuropathy.

The occurrence of peripheral neuropathy in association with autonomic neuropathy is frequent. Forty-two (72.48%) patients have diabetes with autonomic neuropathy had peripheral neuropathy also and the association observed was statistically significant. Ewing et al found that abnormalities occurring in the autonomic nervous system are paralleled by changes in the peripheral nervous system.<sup>20</sup> Subsequently various workers such as Bhatia et al, Patel and Shrivastava have found a correlation between autonomic and peripheral neuropathy.<sup>14,25</sup> Contrary to the above findings in literature, John L et al and Kudrimoti et al did not find any correlation between autonomic neuropathy and peripheral neuropathy.<sup>13,19</sup> Both these studies were done only on patients of type II diabetes mellitus.

The incidence of retinopathy in patients with diabetic autonomic neuropathy was 60.71%. Murray et al have reported high incidence of autonomic neuropathy in patients with proliferative retinopathy.<sup>27</sup> Ewing et al and Kasturi et al have observed a fair correlation between retinopathy and autonomic neuropathy.<sup>20,28</sup> Like retinopathy, nephropathy has been observed to correlate with autonomic neuropathy by various workers in past. In present work nephropathy was seen in 10.34% patients of diabetes autonomic neuropathy. Mani et al commented that autonomic neuropathy is common in patients with renal involvement and may predispose to urinary infection and poor bladder functioning.<sup>29</sup> But Kudrimoti et al<sup>13</sup> did not find any correlation between cardiac autonomic neuropathy and nephropathy

## CONCLUSION

Thus, we conclude that in the present study, the overall prevalence of autonomic neuropathy in diabetes mellitus was 58% at the tertiary care hospital. There was parasympathetic preponderance over sympathetic nervous

system in the involvement of diabetic autonomic neuropathy. There was statistically significant association of diabetic autonomic neuropathy with peripheral neuropathy as compared to retinopathy and nephropathy.

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