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CARDIAC AUTONOMIC DYSFUNCTION IN DIABETES MELLITUS AND ASSOCIATED FACTORS

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ABSTRACT

Background: Autonomic failure is often very disabling in diabetes. Moreover, failure to recognize the symptoms in a diabetic, as due to autonomic neuropathy, may lead to a lot of unnecessary investigations and sometimes, to wasteful treatments. **Material & Methods:** The present prospective study including50 Diabetic patients which were selected by simple random sampling. Institutional Ethics Committee Clearance was obtained and written informed consent was obtained from all the patients. **Results:** Majority 9 (18%) had early cardiac autonomic dysfunction, followed by 4 (8%) had definite, 1(2%) had atypical and severe cardiac autonomic dysfunction respectively. Mean age in cases with autonomic dysfunction was 48.67(S.D. ± 8.25) and 39.17 (S.D. ± 9.34) with no autonomic dysfunction ($p<0.001$).Mean duration of diabetes in cases with autonomic dysfunction was 7.93 (S.D. ± 2.22) and 5.94 (S.D. ± 2.71) with no autonomic dysfunction ($p<0.05$).Mean BMI in cases with autonomic dysfunction was 27.49 (S.D. ± 2.79) and 24.05 (S.D. ± 3.30) with no autonomic dysfunction ($p<0.001$).Among 26 cases with >7 HbA1c, 11 had autonomic dysfunction and 15 cases did not have autonomic dysfunction. Among 24 cases with ≤7 HbA1c, 4 had autonomic dysfunction and 20 did not have autonomic dysfunction ($p<0.05$). **Conclusion:** Incidence of diabetic autonomic dysfunction was more in the age group 41 to 50 yrs. Increased age and body mass index were risk factors for the occurrence of diabetic autonomic dysfunction. Increased duration of diabetes and raised HbA1c value were associated with the occurrence of diabetic autonomic dysfunction.

Keywords: Diabetes, autonomic dysfunction, HbA1c.

INTRODUCTION

Diabetes is now seen as a heterogeneous group of diseases, characterized by a state of hyperglycemia, resulting from a diversity of aetiologies, environmental & genetic, acting jointly**(1)**. Diabetes is a long-term disease with variable clinical manifestations & progression. Chronic hyperglycemia from whatever cause leads to a number of complications:- cardiovascular, renal, neurological, ocular & others such as intercurrent infection **(2)**.

Autonomic neuropathy is the 'needle in the haystack' in the complete evaluation of a diabetic patient. Most clinicians tend to neglect these symptoms even though their patients present only with them. It is indeed a curse for a person to have diabetes but the superimposed impotence or postural syncope may actually worsen his morale on the whole**(3)**. Autonomic neuropathy was only generally recognized as part of the spectrum of nerve damage in diabetes following the work of Jordan in 1936 and Rundles in 1945 **(4)**.

Autonomic failure is often very disabling in diabetes. Moreover, failure to recognize the symptoms in a diabetic, as due to autonomic neuropathy, may lead to a lot of unnecessary investigations and sometimes, to wasteful treatments such as testosterone in sexual impotence and cinnarizine for postural giddiness. A thorough understanding of diabetic autonomic neuropathy on the various systems is a must **(5)**.

It is proclaimed that these bedside methods of assessments calculate the prevalence of autonomic neuropathy in diabetes in a range of 10-100% **(6)**. Thus it is very evident to make an effort to study of autonomic manifestations in diabetes mellitus, and to use the bedside clinical tests to detect early diabetic dystonomia, and the varied relations and effects autonomic failure has on other complications in diabetes **(7).** The present study highlights the direct bearing of diabetic autonomic neuropathy on morbidity and mortality of diabetics, in the form of silent cardiac arrests and the dreaded 'death in bed' syndrome. The significance and need of this study of autonomic manifestations in diabetes mellitus are thus emphasized.

MATERIALS & METHODS

The present prospective study was carried out at Dr. D.Y. Patil Medical College, Hospital & Research Centre, Pimpri, Pune. 50 Diabetic patients were selected for study by simple random sampling. Institutional Ethics Committee Clearance was obtained before the start of the study and written and informed consent for the procedure was obtained from all the patients. Patients with severe anemia, congestive cardiac failure, renal failure, liver diseases, cardiac arrhythmias, pregnant females, age more than 60 years, electrolyte imbalance, central or peripheral neuropathies due to cause other than diabetes and exposure to lead, drugs (like INH) and drugs affecting the autonomic function were excluded from the study. The selected 50 Diabetic patients were questioned about the presence of symptoms reported to be related to autonomic neuropathy, viz. postural giddiness, nocturnal polyuria, disturbances of bladder sphincter, constipation, diarrhea, impotence and bouts of localized sweating. All the patients were subjected to a detailed clinical examination in accordance with proforma. The cases were subjected to five non-invasive autonomic functions tests to assess cardiovascular autonomic reflexes as recommended by Ewing-Clarke which are tests reflecting Parasympathetic functions (heart rate variation during deep breathing, heart rate response to Valsalva Manoeuvre, immediate heart rate response to standing) and tests reflecting Sympathetic functions (blood pressure response to standing, blood pressure response to sustained handgrip). Autonomic dysfunction when present was classified using criteria of Ewing and Clarke **(8)**. The data were analyzed using MS Excel 2010, Epi Info v7 and SPSS v22.

RESULTS

In present study out of total 50 patients, majority 16 (32%) are in the age group 41 to 50 years, followed by 30% who are in the age group 31 to 40 years and 11 (22%) are in age group of 51 to 60 yrs. Only 8 (16%) are in the 21 to 30 yrs. Both males **(25)** and females **(25)** were equal in number in the study group. The majority 9 (18%) had early cardiac autonomic dysfunction, followed by 4 (8%) had definite, 1(2%) had atypical and severe cardiac autonomic dysfunction respectively. 35 cases did not have cardiac autonomic dysfunction in the study group. (Table 1)

Table 1: Incidence of cardiac autonomic dysfunction in the study group

Cardiac Autonomic Neuropathy	No of cases	Percentage
Early	9	18
Atypical	1	2
Definite	4	8
Severe	1	2
No	35	70
Total	50	100

Mean age in cases with autonomic dysfunction was 48.67(S.D. ± 8.25) and 39.17 (S.D. ± 9.34) with no autonomic dysfunction. Z value worked out to be 3.40 which is statistically significant (p<0.001). Mean duration of diabetes in cases with autonomic dysfunction was 7.93 (S.D. ± 2.22) and 5.94 (S.D. ± 2.71) with no autonomic dysfunction. Z value worked out to be 2.71 which is statistically significant (p<0.05). Mean BMI in cases with autonomic dysfunction was 27.49 (S.D. ± 2.79) and 24.05 (S.D. ± 3.30) with no autonomic dysfunction. Z value worked out to be 3.52 which is statistically highly significant (p<0.001). (Table 2)

Table 2: Comparison of parameters with autonomic dysfunction in the study group

Parameter	Autonomic dysfunction				Z Value	P Value
	Yes (n=15)		No (n=35)			
	Mean	SD	Mean	SD		
Age (Yrs)	48.67	8.25	39.17	9.34	3.40	<0.001
Duration (Yrs)	7.93	2.22	5.94	2.71	2.71	<0.05
BMI	27.49	2.79	24.05	3.30	3.52	<0.001

Among 25 males, 8 had autonomic dysfunction and 17 cases did not have autonomic dysfunction. Among 25 females 7 had autonomic dysfunction and 18 did not have autonomic dysfunction (p>0.05). Among 14 cases with type I diabetes 2 cases had autonomic dysfunction and 12 did not have autonomic dysfunction. Among 36 cases with type II diabetes, 13 had autonomic dysfunction and 23 did not have autonomic dysfunction (p>0.05). Among 26 cases with >7 HbA1c, 11 had autonomic dysfunction and 15 cases did not have autonomic dysfunction. Among 24 cases with ≤7 HbA1c, 4 had autonomic dysfunction and 20 did not have autonomic dysfunction, which is statistically significant (p<0.05). Among 34 cases with good compliance 7 cases had autonomic dysfunction and 27 did not have autonomic dysfunction. Among 16 cases with poor compliance 8 had autonomic dysfunction and 8 did not have autonomic dysfunction (p>0.05). Among 19 cases with OHA, 8 had autonomic dysfunction and 11 cases did not have autonomic dysfunction. Among 31 cases with insulin 7 had autonomic dysfunction and 24 did not have autonomic dysfunction (p>0.05). (Table 3)

Table 3: Association between parameters and autonomic dysfunction in the study group

Parameters		Autonomic dysfunction		P value
		Yes	No	
Sex	Male	8	17	>0.05
	Female	7	18	
Type of diabetes	I	2	12	>0.05
	II	13	23	
HbA1c	>7	11	15	**<0.05**
	≤7	4	20	
Currently on OHA/insulin	OHA	8	11	>0.05
	Insulin	7	24	
Compliance	Good	7	27	>0.05
	Poor	8	8	

DISCUSSION

The present study was conducted to find out autonomic dysfunction in diabetic patients and its correlation with age, sex, duration, signs and symptoms and type of diabetes. Total study subjects were 50 cases, which were enrolled based on inclusion and exclusion criteria. Among the incidence of autonomic dysfunction, early cardiac autonomic dysfunction was seen in 18% of cases, 8% of cases

had definite autonomic dysfunction, 2% cases had atypical and severe autonomic dysfunction each. Remaining 70% of cases did not have autonomic dysfunction in the study group.

Age was significantly higher among cases with autonomic dysfunction as compared to cases without autonomic dysfunction in the study group; Mean age was 48.67 in cases with autonomic dysfunction and 39.17 in cases without autonomic dysfunction. A similar finding was also observed in a study conducted by Seung-Hyunko et al (2008) investigated whether cardiovascular autonomic dysfunction was associated with glycemic control status over time in patients with type 2 diabetes. The mean age of cases in study group suffered from diabetic autonomic neuropathy was 53.2 and among cases without autonomic neuropathy were 48.8. The mean difference was statistically highly significant **(9)**.

Sex was not significantly associated with the occurrence of autonomic dysfunction in the study group. A similar finding was observed in a study conducted by Aggarwal S et al, who investigated the incidence of autonomic neuropathy in diabetes and its correlation with age and sex of the patient, duration, and type of diabetes and hyperglycemia. Among 31 males, 22 had autonomic dysfunction and among 19 females 13 had the same. This difference was statistically not significant in the study **(10)**. Type of diabetes was not significantly associated with the occurrence of autonomic dysfunction in the study group. A similar finding was observed in a study conducted by Aggarwal S et al who investigated the incidence of autonomic neuropathy in diabetes and its correlation with age and sex of the patient, duration, and type of diabetes and hyperglycemia. Among 37 cases of Type II diabetes, 26 had autonomic dysfunction and among 13cases with Type I diabetes 9 had the same. This difference was statistically not significant in the study **(10)**.

Duration of diabetes was significantly higher among cases with autonomic dysfunction as compared to cases without autonomic dysfunction in the study group; Mean duration was 7.93 in cases with autonomic dysfunction and 5.94 in cases without autonomic dysfunction. A similar finding was observed in a study conducted by Prabhakar Rao et al intends to detect the prevalence of QTc prolongation in diabetic patients as well as its relationship with cardiac autonomic neuropathy. Duration of diabetes among 70% autonomic neuropathy cases was 5 to 10 years. Only 14% cases had a duration of diabetes less than 5 yrs and 16% cases had a duration of diabetes more than 10% **(11)**.

Piyali Das et al assessed different cardiovascular autonomic function parameters like change of blood pressure from supine to standing posture (postural BP changes) and ratio of longest and shortest R-R interval during deep expiration and inspiration respectively (E/I ratio) on ECG in type 2 diabetics, duration of diabetes, HbA1c and age sex-matched non diabetic controls. Duration of diabetes was not significantly associated with autonomic dysfunction in the study which did not resemble with our study finding **(12)**. Nazeema Khatoon et al evaluate and correlate the cardiovascular autonomic neuropathy using simple Ewing's tests with QTc interval in diabetic patients. Results showed that diabetics had significantly impaired cardio-autonomic reflexes compared to non-diabetics, which increases with the duration of diabetes**(13)**.

Patients taking oral hypoglycemic drugs or insulin were not significantly associated with the occurrence of autonomic dysfunction in the study group. Poor compliance for treatment was significantly associated with autonomic dysfunction in the study group. Abnormal BMI was significantly associated with autonomic dysfunction among cases in a study group with diabetes compared to those who were not having autonomic dysfunction. A similar finding was also observed in the study conducted by Elisabeth Gulichsen et al who evaluated the prevalence of cardiac autonomic neuropathy diagnosed by reduced heart rate variability (HRV) in a hospital-based population of patients with diabetes. BMI was 28.9 among the cases with autonomic dysfunction and 27.1 in normal cases; this difference was statistically significant in the study **(14)**.

Raised HbA1c was significantly associated with autonomic dysfunction in the study group. Kempler P et al (2002) assessed the prevalence and risk factors

for autonomic neuropathy in the EURODIAB IDDM Complications Study. The prevalence of autonomic neuropathy was 36% with no sex differences out of 3007 patients. Significant correlations were observed between autonomic neuropathy and age ($P < 0.01$), duration of diabetes ($P < 0.0001$), HbA1c ($P < 0.0001$) **(15)**.

CONCLUSION

We concluded from the present study that incidence of diabetic autonomic dysfunction was more in the age group 41 to 50 yrs. Increased age and body mass index were risk factors for the occurrence of diabetic autonomic dysfunction. Increased duration of diabetes and raised HbA1c value were associated with the occurrence of diabetic autonomic dysfunction.

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