

Correlation Between Cognitive Dysfunction and Cardiac Autonomic Dysfunction in Patients with T2DM In a Tertiary Care Medical Institute of South India

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ABSTRACT

Background: Diabetes mellitus is a non-communicable disease that has a high prevalence in our country and is known for causing both microvascular and macrovascular complications. Cognitive dysfunction is one such complication with higher incidence of cognitive impairment in diabetes patients compared to subjects without diabetes. Its pathophysiology may not be clear but may be attributed to defects in insulin signalling and neuroinflammatory pathways. It also causes autonomic dysfunction which is implicated for cardiovascular complications in diabetes resulting due to lesions in the sympathetic and parasympathetic nerve fibres. These two neurological complications can be associated with long standing hyperglycemia.

Objective: The objective of the study is to find the correlation between cardiac autonomic dysfunction and cognitive impairment.

Material and Methods: A total of 99 patients between 18-60 years under both OP and IP care were examined after excluding patients with known vascular complications, psychiatric illnesses, acute illness, smoking, alcoholism, hypertension, cardiovascular and neurological diseases. The detailed history of the patient was taken including the treatment history to know the duration of the disease and whether the patient was on OHAs or insulin. MMSE was done to assess the cognitive function of the patients. The Autonomic function was assessed by performing valsalva maneuver, isometric handgrip, looking for heart rate variation with deep breathing, orthostatic BP assessment and looking for resting tachycardia.

Results: The prevalence of cognitive impairment was found to be 42.42% and autonomic dysfunction was 90.90% respectively. Both these complications were found to have a strong association with duration of diabetes. A strong association was also found between sex and autonomic dysfunction while no such association was found between cognitive impairment and sex of an individual. Higher incidence of autonomic dysfunction was seen among the patients who were on insulin. Family history was also seen to be associated with cognitive impairment. Significant correlation between Cognitive dysfunction and autonomic dysfunction was established via this study.

Conclusion: A very high prevalence of autonomic dysfunction was seen in the patients suffering from diabetes and almost half of them suffered from mild cognitive impairment with significant association between the two variables.

Keywords: Cognitive dysfunction, Autonomic dysfunction, Diabetes mellitus, microvascular, cardiovascular complications, MMSE, Valsalva maneuver.

INTRODUCTION

India is well known as the Diabetic capital of the world with its rapidly escalating prevalence rates rising from less than 3% in 1970 to 7.2% in 2019 with 62 million people suffering from the disease.^[1,2] The rapid socioeconomic transition and the increased genetic susceptibility of the Indian population along with the unhealthy high calorie diets and sedentary lifestyle has made the country one of the epicentres of the global DM pandemic.^[3,4]

The term 'diabetes' describes a group of metabolic disorders characterized and identified by the presence of hyperglycaemia in the absence of treatment. The heterogeneous aetio-pathology includes defects in insulin secretion, insulin action, or both, and disturbances of carbohydrate, fat and protein metabolism. Diabetes is classified into two types, with type 2 also called non-insulin dependent diabetes mellitus primarily caused due to various degrees of β -cell dysfunction and insulin resistance ; commonly associated with overweight and obesity.^[5] With diabetes being known as the disease of the vasculature, it leads to both microvascular and macrovascular complications as the disease progresses.^[6,7,8]

This comprises of significant complications of the central nervous system, also called 'Diabetic encephalopathy'.^[9] One such complication is the reduced performance on multiple domains of cognitive function due to the structural abnormalities in the brain. Recent studies indicate a higher incidence of mild cognition impairment in diabetic patients compared to the individuals without diabetes.^[10] It also significantly increases the risk of Alzheimer's disease.^[11] Even with the pathophysiology not completely explained, defects in insulin signalling, neuro inflammatory pathways, mitochondrial metabolism, the accumulation of advanced glycation end-products (AGEs) and oxidative stress are known to contribute to this dysfunction.^[12,13] The severe cognitive dysfunction is also known to be associated with poorer self care in the diabetes patients leading to a deterioration in the quality of their daily life.^[14]

One of the other most common but often underestimated neural complications is the autonomic dysfunction of the cardiovascular system. The primary extrinsic control mechanism that regulates the heart rate and cardiac performance is the autonomic innervation. Chronic hyperglycemia induces autonomic neural dysfunction resulting in cardiovascular autonomic neuropathy which leads to increased cardiovascular mortality.^[15,16]

This dysfunction usually manifests as mild arrhythmias to sudden death.^[17] The severity of the dysfunction is found to have significant correlation with the HbA1C levels.^[18]

With the prevalence of type 2 DM in the adolescents and young adults dramatically increasing, they are in a higher risk for such chronic but often overlooked complications such as cognitive impairment and autonomic dysfunction.^[20] Hence we attempt to find the correlation between the pathophysiology of the autonomic dysfunction and cognitive dysfunction due to the common central nervous system involvement. Even though peripheral neuropathy is routinely assessed, the cognitive and autonomic dysfunction is often understated and needs to be given equal relevance.

Objectives

- To find the correlation between cardiac autonomic dysfunction and cognitive impairment.
- To find the association between neurological dysfunctions and the duration of diabetes

MATERIAL & METHODS

Study Design

The study was a Descriptive Cross sectional study which was conducted in Department of Internal Medicine (both OP and IP patients), Amala Institute of Medical Sciences, Thrissur, Kerala during the period of August 2019 to July 2022. The patients who were selected for the study were known or newly diagnosed patients of Type 2 Diabetes mellitus according to the ADA^[22] criteria who were under OPD care and IP care. These patients included all males and females between the ages 18 – 60 years without any age-related cognitive impairment. Any patients who previously had stroke, has any psychiatric illnesses or an acute illness or patients with smoking, alcoholism, hypertension, cardiovascular diseases and neurological diseases were excluded from the study. The sample size of the study was 99 with 51 males and 48 females participating in the study. Consecutive sampling method was used. Informed consent was obtained from all the participants. The detailed history of the patient is taken including the treatment history (OHAs and insulin) and the duration of diabetes. MMSE was done to assess the cognitive function of the patients. The Autonomic function was assessed by a series of clinical examination methods such as valsalva maneuver, isometric handgrip & looking for heart rate variations with deep breathing, orthostatic hypotension and resting tachycardia. The study was approved by the institutional research committee and ethics committee.

Diagnosis of Cognitive Impairment

The cognitive function of the patient was assessed using the MMSE^[23] scale. The Mini-Mental State Examination (MMSE) is a widely used test of cognitive function among the elderly; it includes tests of orientation, attention, memory, language and visual-spatial skills with scoring as follows. Orientation (10 points), Registration (3 points), Attention and Calculation (5 points), Recall (3 points), Language and Praxis (9 points). The questionnaire comprises of 11 questions assessing a patient based on the above parameters with a total score of 30. A subject scoring less than 24 in this test is said to have mild cognitive impairment and a score less than 18 is indicative of severe cognitive deficit. The subject's educational level was also considered with a cut-off point of less than 21 for 8th grade education, cut off point of less than 23 for high school education and less than 24 for college education.

Diagnosis of Cardiac Autonomic Dysfunction

The autonomic function of the patient was assessed by the following clinical examination methods.

- **VALSALVA MANEUVER^[24]**: In the valsalva maneuver, the subject exhales against a closed glottis or into a manometer for 10 to 15 s, creating a markedly positive intrathoracic pressure. The sharp reduction in venous return to the heart causes a drop in cardiac output and in blood pressure; the response on baroreceptors is to cause a reflex tachycardia and, to a lesser extent, peripheral vasoconstriction. With release of intrathoracic pressure, the venous return, stroke volume, and blood pressure rise to higher-than-normal levels; reflex parasympathetic influence then predominates and a bradycardia results. Failure of the heart rate to increase during the positive intrathoracic phase of valsalva maneuver points to sympathetic dysfunction, and failure of the rate to slow during the period of blood pressure overshoot points to a parasympathetic disturbance. In patients with autonomic failure, the fall in blood pressure is not aborted during the last few seconds of increased intrathoracic pressure, and there is no overshoot of blood pressure when the breath is released.
- **ISOMETRIC HANDGRIP^[25]**: The sustained isometric contraction of the group of muscles in the forearm in handgrip for 5 min normally increases the heart rate and the

systolic and diastolic pressures by atleast 15 mm Hg. The response is reduced or absent with lesions of the sympathetic reflex arc, particularly of the efferent limb.

- **ORTHOSTATIC HYPOTENSION^[26]**: This type of syncope is the result of orthostatic loss of blood pressure. It affects patients whose adrenergic innervation to the blood vessels is defective or those who are hypovolemic. The patient with autonomic failure, on assuming an upright position, shows a steady decline in blood pressure that begins almost immediately and, if not checked, declines to a level at which the cerebral circulation cannot be supported. The bedside testing of orthostatic blood pressure is performed by having the patient stand quickly and taking readings immediately and again at 1 min and at 3 min.
- **DEEP BREATHING^[27]**: The vagal function is purely quantitated by measuring the variation in heart rate during deep breathing (respiratory sinus arrhythmia). The patient is made to breathe at a regular rate of 6 breaths per minute. Normally, the heart rate varies by as many as 15 beats per minute or more between inspiration and expiration. Differences of less than 7 beats per minute for ages 60 to 69 and 9 for ages 50 to 59 may be abnormal.
- **RESTING TACHYCARDIA^[28]**: Resting heart rates of 100 bpm with occasional increments up to 130 bpm reflects a relative increase in the sympathetic tone associated with vagal impairment. A fixed heart rate that is unresponsive to moderate exercise, sleep or stress is indicative of severe cardiac autonomic neuropathy.
- Any abnormality in the above clinical examination methods was considered as a sign of autonomic dysfunction and was used in the diagnosis of the same.

Data Analysis

The data obtained was entered in MS Excel worksheet and worksheet analysis was done using the SPSS software version 23. Prevalences of cognitive impairment and autonomic dysfunction were calculated. The correlation between the two variables was calculated using the Pearson correlation test. The associations between the sociodemographic factors and cognitive dysfunction as well as autonomic dysfunction were calculated using the chi-square test and $p < 0.05$ was considered to be significant.

RESULTS

In this study, 99 subjects were evaluated for cognitive impairment and autonomic dysfunction out of which 51 (51.51 %) were males and 48 (48.49 %) were females. The mean age of the study population was 50.97 +/- 8.36 (mean +/- SD). Out of the 99 diabetic patients, 45 (45.45 %) of them were currently using insulin while the rest 54(54.5%) patients were on OHAs. In the study, 63 (63.64 %) out of total 99 subjects had a positive family history which indicates that the majority of people suffering from the disease may have a genetic predisposition. Of the total 99 patients, 33 (33.34%) of them only suffered the disease for < 5years while only 6 patients have been suffering the disease for 30-35 years. The mean duration of illness was 10.616 +/-8.76. The prevalence of patients diagnosed with peripheral neuropathy was found to be 18.2%. The prevalence of patients with diabetic retinopathy and diabetic nephropathy was calculated to be 15.2% and 27.3% respectively.

It was found during the study that 42(42.4%) out of 99 subjects suffered from cognitive deficit out of which 39 (39.4%) was diagnosed with mild cognitive impairment while 3(3.03%) of the patients suffered from severe cognitive deficit. The average MMSE score obtained by the patients was 24.45 +/- 3.47. The association between cognitive impairment and duration was assessed using the chi-square test and p-value obtained was less than 0.05. Hence there is very strong evidence of an association between Cognitive impairment and duration of diabetes. Furthermore, cognitive impairment and family history of diabetes

has association with each other while there was no significant association between sex and cognitive impairment. It was also observed that the prevalence of cognitive impairment among subjects using insulin was 46.67%. The attention and calculation component was the most severely affected in most patients while praxis was the least affected.

The prevalence of autonomic dysfunction among the study population was 90.9%, that is most of the subjects were tested positive for autonomic dysfunction. The association between autonomic dysfunction and duration of diabetes was also assessed and p-value (0.030) was smaller than the standard alpha value (0.05) and hence concluded to be significant. Autonomic dysfunction was also found to be associated with the sex of the individual according to the chi-square test. 42(93.3%) out of the 45 subjects on insulin were also found to be suffering from autonomic dysfunction. The clinical test that became positive in majority of the patients was Valsalva maneuver.

The correlation between cognitive impairment and autonomic dysfunction was assessed in these 99 subjects. Pearson correlation between autonomic dysfunction and cognitive impairment is 0.271, even though it shows low degree positive correlation but it is still significant since $0.007 < 0.05$ (alpha value). Hence it is proved that there is a significant correlation between Cognitive impairment and autonomic dysfunction in diabetic patients.

Severity Grading	MMSE Score	No. Of patients	Percentage
Severe	0-17	3	3.03
Mild	18-23	39	39.4
Normal	24-30	57	57.6

Autonomic Dysfunction * Duration of Diabetes Cross Tabulation

		Duration of Diabetes						Total	
		0-5	5-10	10-15	15-20	25-30	30-35		
Autonomic Dysfunction	N	Count	6	0	0	3	0	0	9
		% of Total	6.1%	0.0%	0.0%	3.0%	0.0%	0.0%	9.1%
	Y	Count	27	18	21	9	9	6	90
		% of Total	27.3%	18.2%	21.2%	9.1%	9.1%	6.1%	90.9%
Total		Count	33	18	21	12	9	6	99
		% of Total	33.3%	18.2%	21.2%	12.1%	9.1%	6.1%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	12.375a	5	.030
Likelihood Ratio	15.529	5	.008
N of Valid Cases	99		

a. 6 cells (50.0%) have expected count less than 5. The minimum expected count is .55.

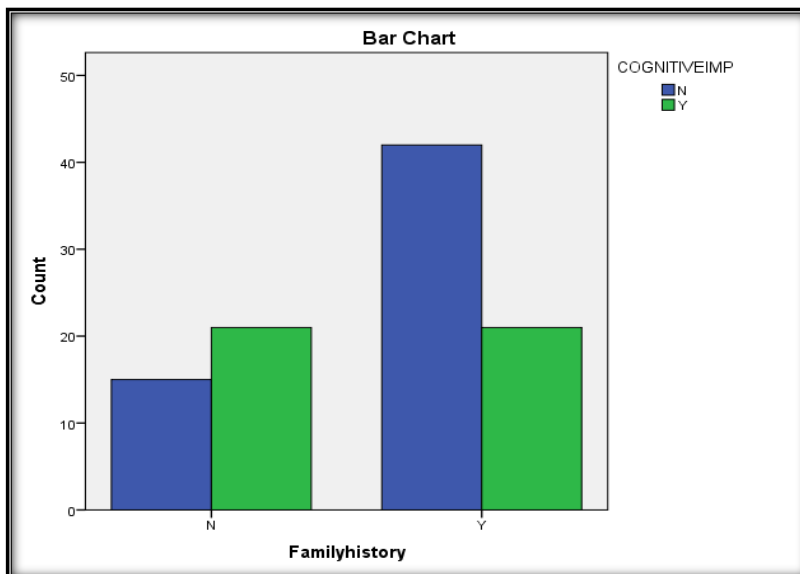
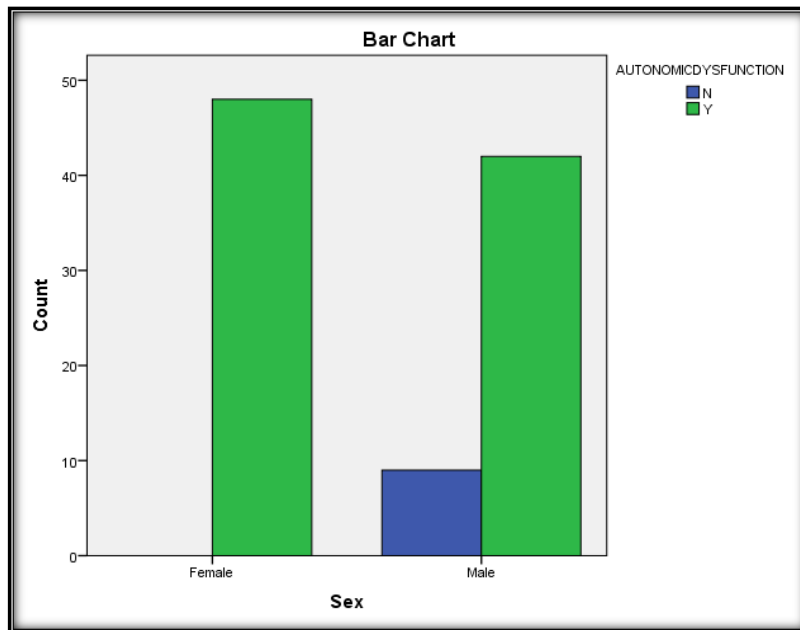
Cognitive impairment * duration of diabetes cross tabulation

		Duration of Diabetes						Total	
		0-5	5-10	10-15	15-20	25-30	30-35		
Cognitive Impairment	N	Count	21	12	9	9	0	6	57
		% of Total	21.2%	12.1%	9.1%	9.1%	0.0%	6.1%	57.6%

	Y	Count	12	6	12	3	9	0	42
		% of Total	12.1%	6.1%	12.1%	3.0%	9.1%	0.0%	42.4%
Total		Count	33	18	21	12	9	6	99
		% of Total	33.3%	18.2%	21.2%	12.1%	9.1%	6.1%	100.0%

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	21.095a	5	.001
Likelihood Ratio	26.607	5	.000
N of Valid Cases	99		

a. 3 cells (25.0%) have expected count less than 5. The minimum expected count is 2.55.



		Autonomic Dysfunction	Cognitive Impairment
Autonomic Dysfunction	Pearson Correlation	1	.271**
	Sig. (2-tailed)		.007
	N	99	99
Cognitive Impairment	Pearson Correlation	.271**	1
	Sig. (2-tailed)	.007	
	N	99	99
**. Correlation is significant at the 0.01 level (2-tailed).			

DISCUSSION

The prevalence of cognitive impairment in the 99 study subjects was 42.4% out of which 92.8% only suffered from mild cognitive impairment while the rest 7.2% suffered from significant cognitive impairment. A study conducted in Kerala by Sangeetha Merrin Varghese^[29] et al showed that 63.8% among the diabetic patients suffered from cognitive impairment. Almost half of the diabetics in our study suffered from the impairment. In a study conducted in Poland by Malgorzata Gorska-Ciebiada^[30] et al, the prevalence of mild cognitive impairment was 31.5%. We found a significant association between cognitive impairment and duration of diabetes. In the study by Sangeetha Merrin Varghese^[29] et al, the duration of diabetes played a significant role in Cognition with the mean duration of diabetes being higher in patients with cognitive impairment. The study conducted by D.G Bruce^[32] et al also demonstrates duration of diabetes as an independent predictor of dementia. In our study, no significant association was proved between cognitive impairment and sex of the individual and the above study by Sangeetha et al also could not prove any statistical significant relationship between the two variables. However in a study conducted in Punjab by Shallu Khullar^[31] et al it was demonstrated that being a woman is an independent predictor of cognitive decline. Our study also proves a significant association between cognitive impairment and family history of diabetes and may point towards a genetic component in the evolution of dementia. In our study, most subjects were found to have deficit in attention and calculation while the study by Sangeetha^[29] et al exhibited most decline in the visuo-spatial domain and the least affected was memory.

In our study, a vast majority of 90.9% tested positive for autonomic dysfunction. This is comparatively high compared to other studies. In a study conducted in South India by V. Mohan^[33] et al, the prevalence rate of autonomic dysfunction in non-insulin dependant diabetic patients was calculated to be 35.7% while in another study by I.A.D. O'Brien N^[34] et al, the prevalence rate of autonomic neuropathy in insulin dependent diabetic patients was calculated as 16.6%. Autonomic neuropathy was shown to have a significant association with duration of diabetes and a similar result was also obtained in the study by I.A.D.O'Brien N et al. 53.3% of the subjects suffering from autonomic dysfunction are females while the rest 46.7% are males and even though the difference is small, a significant association between sex of the individual and autonomic dysfunction is also proved. However in a study by L.Barkai^[35], it was demonstrated that there is no significant association between the two variables. A high proportion of subjects on insulin, that is, 93%, were tested positive for autonomic dysfunction which may be one indication that glycemic control plays an important role in the progression of autonomic neuropathy.

The study demonstrates that a positive correlation exists between autonomic dysfunction and cognitive impairment in a patient suffering from Type 2 diabetes mellitus. A similar result was demonstrated by a study in JIPMER conducted by Pal Auroprajna^[21] et al. Hence these two neurological complications of diabetes may co-exist in a patient with diabetes and even

though one is a complication of central nervous system and other of the peripheral autonomic nervous system, this association may point towards a similar basis of pathophysiology that may need further studies.

CONCLUSION

This study evaluated two neurological complications of diabetes that are often overlooked, that is, cognitive impairment and autonomic dysfunction. Autonomic dysfunction in a patient predisposes them to cardiovascular co-morbidities and mortality. Mild cognitive impairment in such diabetic patients might often predispose the patients to dementia and Alzheimers. Detection of these deficits at an earlier stage might help the clinician to slow down the progress of the disease and to aim at a better glycemic control. More studies need to be done to understand the pathophysiology and mechanism of both of these complications better, with emphasis on better diagnostic and therapeutic measures and while it may not be practical to assess for autonomic and cognitive function at every routine visit, these assessments can be done yearly or at regular intervals as a part of routine screening similar to diabetic retinopathy and nephropathy. It is high time we enlist these complications along with the known complications of the disease such as peripheral neuropathy and retinopathy since these complications heavily contribute to the mortality and causes significant morbidity. And since these two complications may be associated with each other, diagnosis of the former should arouse suspicion of the latter and vice versa. The studies and research in these areas are still lacking and more research is required for better management and rehabilitation of such patients

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