

Comparison of Cardiovascular Autonomic Neuropathy (CAN) in Type 2 Diabetes Mellitus with and without Gastro Esophageal Reflux Diseases

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ABSTRACT

Background: Autonomic nervous system dysfunction is quite common yet often unrecognized. Recently the researcher found that the Cardiovascular Autonomic Neuropathy (CAN) is an early and recurrent complication of diabetes mellitus with an account of 7-15 % in newly diagnosed cases. On the other hand the complication of Gastro esophageal reflux diseases is increased among the uncontrolled diabetes mellitus patients because the transient lower esophageal sphincter relaxation. Not much awareness about the T2DM with GERD group and none of the study showed clear evidence between the diabetes mellitus with GERD and autonomic dysfunction.

Materials and Methods: Group 1 includes 40 Type 2 diabetes mellitus patients (T2DM) and group 2 includes 40 Type 2 diabetes mellitus with Gastroesophageal reflux diseases (T2DM with GERD). We analyzed the status of sympathetic and parasympathetic nervous system on heart by using Ewing's cardiovascular autonomic nerve function test in these 2 groups. Qualitative data was analyzed by Chi Square test which express the frequency and percentage of the data.

Results: Our study showed that, in both the group the maximum number of CAN was distributed in the range of HbA1c > 8 with the percentage of 30 in diabetes mellitus group and 42.5 percent in diabetes mellitus with GERD group where as the percentage was more in later group.

Conclusion: We have highly recommended the clinician to check the degree and severity of cardiovascular autonomic neuropathy in diabetes patients with and without GERD by a simple non-invasive technique with Ewing's cardiovascular autonomic function test for the betterment of patient's life.

Keywords: Cardiovascular autonomic neuropathy, type 2 diabetes mellitus, gastro esophageal reflux diseases

INTRODUCTION

Autonomic nervous system dysfunction is quite common yet often unrecognized. Recently there has been an increased awareness of the role of autonomic nervous system action in the diversity of diseases. Effect of autonomic testing can be significant tool for evaluation of these disorders.^[1] There are various autonomic tests, however, only some were validated clinically or quantitative. These techniques most generally utilized in the clinical setting helps to measure the associated degree, severity and incidence of end-organ response to a physiological provocation.^[2] Altered autonomic activities associated with variety of disorders since ANS regulates

the blood pressure (BP), respiration, gut, heart, and vascular tone which help to adapt various organs to environmental and psychological challenges.^[3-5] Heart and blood vessels is innervated by autonomic nerves, damage to that nerve fibre leads to cardiovascular autonomic Neuropathy (CAN) which shows the abnormalities in heart rate control and vascular dynamics.^[6]

Previously many studies reported that the complications of cardiovascular autonomic neuropathy takes place in the later stage or chronic diabetes mellitus patients. But recently the researcher found that the CAN is an early and recurrent complication of diabetes mellitus with an

account of 7-15 % in newly diagnosed cases.^[7] This could be most disable and life threatening complication in diabetes mellitus. On the other hand the complication of Gastro esophageal reflux diseases is increased among the uncontrolled diabetes mellitus patients because the transient lower esophageal sphincter relaxation is found more frequently in diabetes mellitus patients.

Transient lower esophageal sphincter relaxation is well known pathogenic factor for GERD which is controlled through vagal activity^[8] and this could be an clarification how gastroesophageal reflux is related to the autonomic neuropathy in Diabetes Mellitus.^[9,10] Though GERD is a risk factor in diabetic patients, GERD is itself a major clinical disorder that should be to be treated and diagnosed separately.

Not much awareness about the T2DM with GERD group and none of the study showed clear evidence between the diabetes mellitus with GERD and autonomic dysfunction. Thus in our study we assessed the linkage of autonomic nervous system between diabetes and GERD with cardiovascular impairment analyzed by cardiovascular autonomic function tests.

MATERIALS AND METHODS

This observational study included 80 patients and it was categorized in to 2 groups. Group 1 includes 40 Type 2 diabetes mellitus patients (T2DM) and group 2 includes 40 Type 2 diabetes mellitus with Gastroesophageal reflux diseases (T2DM with GERD).

This study was carried out in the Department of Physiology, SRM Medical College Hospital and Research Center, Tamil Nadu. This study was approved by the Institutional Ethics Committee, SRM Medical College Hospital and Research Center. The Ethical clearance number was 783/IEC/2015.

We included male and female type 2 diabetes mellitus with and without GERD with age group of 30-60 and we excluded the habitual smokers, patients with Angina pectoris, arrhythmia, chronic obstructive pulmonary disease, asthma, sinusitis, previous upper GI surgery, patients in taking drugs like nitrites, β -blockers, calcium channel antagonists, non-steroidal anti-inflammatory drugs and antioxidant supplements.

After collecting the detail history of the patients, we analyzed the status of sympathetic and parasympathetic nervous system on heart by using Ewing's cardiovascular autonomic nerve function test. It was a simple non invasive technique which consists of following battery of test.

Heart rate response to deep breathing, Heart rate response to valsalva maneuver, and Heart rate response to lying to standing test which illustrate the parasympathetic activity on heart, and Blood pressure response to lying to standing and Blood pressure response to Hand grip test to assess the sympathetic activity on heart. Both the test helps to assess the integrity, dysfunction, severity, degree and status of cardiovascular autonomic nervous system. Cardiovascular autonomic neuropathy was interpreted based on two criteria:

1. As per Ewing's criteria
2. As per AIIMS AFT Lab Criteria.

Interpretation of CAN as per Ewing's criteria^[11]:

Normal	= All tests normal or 1 test borderline.
Early	= One of the three heart rate tests abnormal or two borderline.
Definite	= Two heart rate tests abnormal.
Severe	= Two heart rate tests abnormal + one or both BP tests abnormal or both borderline
Atypical	= any other combination of abnormalities

Interpretation of CAN as per As per AIIMS AFT Lab criteria:

Score for parasympathetic and sympathetic component separately.

Normal	= All tests normal or 1 test borderline.
Early	= One of test abnormal or two tests borderline.
Definite	= Two tests abnormal.

STATSTICAL ANALYSIS

Statistics were held with SPSS software (SPSS 16.0 for Windows, IBM Co). Qualitative data was analyzed by Chi Square test which express the frequency and percentage of the data. Quantitative data was expressed as Mean and standard deviation which was analyzed by student independent t test. The level of significance was set at *P < 0.05 and ***P<0.01.

Table 1: Comparison of blood glucose level and HbA1c between diabetes mellitus and diabetes mellitus with GERD

Parameter	T2DM alone Mean \pm SD	T2DM with GERD Mean \pm SD	t value	Sig
Fasting blood glucose	168 \pm 41.3	185 \pm 32.9	2.07	.042*
Post prandial glucose	242 \pm 59.8	240 \pm 45.1	.798	.35(ns)
HbA1c	8.03 \pm 1.58	8.6 \pm 1.41	1.92	.058*
Duration of diabetes	8.17 \pm 2.77	8.28 \pm 3.56	0.1262	.899 (ns)

RESULTS

Values are expressed in Mean \pm SD; SD-Standard Deviation, Independent student -'t' test, *p<0.05- **p<0.01- statistically significant, NS-not significant, GERD-Gastro esophageal reflux diseases, HbA1c-Glycosylated haemoglobin.

Table 1 showed the fasting blood glucose and HbA1c of diabetes mellitus with GERD patients had significantly higher value when compared to diabetes mellitus patients group. But both the value had higher than normal range. The post prandial blood glucose was not statistically difference between diabetes mellitus and diabetes mellitus with GERD. The duration of diabetes was not statistical significant, and it was vary from 1-14 years among the two diabetic groups.

Based on Ewing's criteria the cardiovascular autonomic neuropathy was classified as normal, early, definite and severe. Table 2 showed that 32.5 % of Diabetes mellitus group were normal, whereas 42.5% had early, 22.5% had definite and 2.5 % had severe cardiovascular autonomic neuropathy. In Diabetes mellitus with GERD group 25 % of patients were normal, whereas 47.5% had early, 17.5% had definite and 10% had severe cardiovascular autonomic neuropathy.

According to AIIMS AFT LAB criteria the cardiovascular

Table 2: Comparison of cardiovascular autonomic neuropathy (CAN) based on Ewing's criteria between T2DM alone and T2DM with GERD by using chi –square test

Category	T2DM alone N (%)	T2DM with GERD N (%)	Total N (%)
Normal	13(32.5)	10(25)	23 (28.8)
Early	17(42.5)	19(47.5)	36 (45)
Definite	9(22.5)	7(17.5)	16 (20)
Severe	1(2.5)	4(10)	05 (6.2)
Total	40 (100)	40 (100)	80 (100)

autonomic neuropathy was classified as normal, early and definite separately for parasympathetic and sympathetic nervous system. In Table 3 explained that the Diabetes mellitus group contained 32.5 % of normal parasympathetic activity, 42.5% of early parasympathetic dysfunction and 25 % of definite parasympathetic dysfunction whereas 75 % of normal sympathetic activity, 22.5 % of early sympathetic dysfunction and 2.5 % of definite sympathetic dysfunction. In Diabetes mellitus with GERD group contained 25% of normal parasympathetic activity, 47.5% of early parasympathetic dysfunction and 27.5% of definite parasympathetic dysfunction whereas 65 % of normal sympathetic activity, 27.5 % of early sympathetic dysfunction and 7.5 % of definite sympathetic dysfunction.

Table 3: Comparison of cardiovascular autonomic neuropathy (CAN) based on AIIMS AFT LAB between T2DM alone and T2DM with GERD by using chi –square test

Category	T2DM alone N (%)		T2DM with GERD N (%)	
	Parasympathetic	Sympathetic	Parasympathetic	Sympathetic
Normal	13(32.5)	30(75)	10(25)	26(65)
Early	17(42.5)	9(22.5)	19(47.5)	11(27.5)
Definite	10(25)	1(2.5)	11(27.5)	03(7.5)
Total	40 (100)	40 (100)	40 (100)	40 (100)

Table 4: Comparison of duration of diabetes and CAN between diabetes mellitus and diabetes mellitus with GERD group by using chi –square test

Duration of Diabetes mellitus	T2DM alone N (%)		T2DM with GERD N (%)	
	N (%)	CAN = N(%)	N (%)	CAN = N (%)
0-5 years	18(45)	10(25)	11(27.5)	08(20)
5-10 years	14(35)	09(22.5)	14(35)	10(25)
>10 years	08(20)	06(15)	15(37.5)	13(32.5)

We categorized the duration of diabetes in to three group- 0-5 years, 5-10 years and >10 years. In our study Table 4 illustrated that the maximum number diabetic cases seen in 0-5 years was about 45% where as 35% seen in 5-10 years and 20% cases was seen in >10 years with the incidence rate of CAN was about 25%, 22.5% and 15 %

respectively.

The maximum number of diabetics with GERD group was seen in >10 years with the incident rate of CAN of about 32.5% followed by 35 % cases seen in 5-10 years with 25% of CAN and 27.5 % of cases seen in 0-5 years with 20% of CAN.

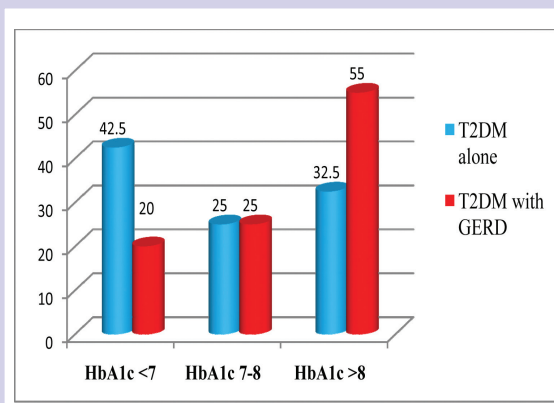


Figure 1: Distribution of cases over different range of HbA1c between two diabetic groups

We categorized the HbA1c in to three group- HbA1c <7, HbA1c 7-8 and HbA1c >8. From figure 1 we clearly know that the maximum number of diabetic patients was seen in the range of HbA1c <7 of about 42.5% whereas 25% of cases was seen in the range of HbA1c 7-8 and 32.5% of cases was seen in the range of >8 and in diabetic patients with GERD group the maximum number of patients was seen in HbA1c >8 where as 25% of cases was seen in the range of HbA1c 7-8 and 20% of cases was seen in the range of <7.

Table 5 showed that the incidence rate of CAN was about 20% in diabetic group in the range of HbA1c <7 where as 17.5% of CAN in the range of HbA1c 7-8 and 30% of CAN in the range of HbA1c >8.

In diabetic with GERD group the incidence rate of CAN is about 15% in the range of HbA1c <7 where as 17.5% of

Table 5: Distribution of CAN over different range of HbA1c among diabetes mellitus groups

HbA1c(total no. of patients)	CAN / No CAN	T2DM alone N (%)		
		Ewing's criteria	Parasympathetic neuropathy	sympathetic neuropathy
HbA1c <7(17)	CAN	8(20)	8(20)	2(5)
	No CAN	9(22.5)	9(22.5)	15(37.5)
HbA1c 7-8 (10)	CAN	7(17.5)	7(17.5)	3(7.5)
	No CAN	3(7.5)	3(7.5)	7(17.5)
HbA1c >8 (13)	CAN	12(30)	12(30)	5(12.5)
	No CAN	1(2.5)	1(2.5)	8(20)
Total (40)		40(100)	40(100)	40(100)

Table 6: Distribution of CAN over different range of HbA1c among diabetes mellitus with GERD groups

HbA1c (total no. of patients)	CAN / No CAN	T2DM with GERD N (%)		
		Ewing's criteria	Parasympathetic neuropathy	sympathetic neuropathy
HbA1c <7(8)	CAN	6(15)	6(15)	3(7.5)
	No CAN	2(5)	2(5)	5(12.5)
HbA1c 7-8 (10)	CAN	7(17.5)	7(17.5)	4(10)
	No CAN	3(7.5)	3(7.5)	6(15)
HbA1c >8 (22)	CAN	17(42.5)	17(42.5)	7(17.5)
	No CAN	5(12.5)	5(12.5)	15(37.5)
Total (40)		40(100)	40(100)	40(100)

CAN in the range of HbA1c 7-8 and 42.5% of CAN in the range of HbA1c >8 which was illustrated in table 6.

DISCUSSION

Cardiovascular autonomic neuropathy (CAN) is the most important life threatening complication which affects the regulatory capacity of heart rate and vascular dynamics

leads to severe morbidity and mortality. It has strong influence on various cardiovascular disorders like arrhythmia, pain less myocardial ischemia, myocardial infarction, orthostatic hypotonia and sudden cardiac death where as the early diagnosis of CAN reduce this disorder.^[12]

CAN is commonly seen in diabetes mellitus patients and

Gastroesophageal reflux diseases (GERD) but it is under diagnosed. Therefore the ADA (American Diabetes Association) has strongly recommended diagnosing the CAN as a routine screening procedure for diabetes as well as diabetes with other complications.

The ADA is highly recommended the gold standard Ewing's battery test and HRV to assess the cardiovascular autonomic neuropathy.^[13] It consist of 5 non invasive battery test in clinical practice is considered as the corner stone for diagnosis the cardiovascular autonomic neuropathy (CAN). It widely assess the status of parasympathetic reactivity by heart rate response to deep breathing, Valsava maneuver and Lying to standing and sympathetic reactivity by blood pressure changes in lying to standing and isometric hand grip test.

Cardiovascular autonomic neuropathy is an important reason for cardiovascular mortality which is frequently associated with T2DM. Now a day it is highly recommended to screen the CAN in T2DM.^[11]

In our study based on Ewing's criteria 32.5 % of diabetic patients were normal, whereas 42.5% had early, 22.5% had definite and 2.5 % had severe cardiovascular autonomic neuropathy. Based on AIMS AFT criteria, 32.5 % of diabetic patients were normal parasympathetic activity where as 42.5% of early parasympathetic dysfunction and 25 % of definite parasympathetic dysfunction and 75 % of diabetic patients were normal sympathetic activity, 22.5% of early sympathetic dysfunction and 2.5 % of definite sympathetic dysfunction.

We observed that the overall prevalence rate of CAN in diabetes mellitus is about 67.5% but Mehta et al^[14], and Behera et al^[15] found that little lesser prevalence rate of CAN in diabetic patients. Behera et al stated that the incidence rate of CAN in T2DM was 57.5 % and Mehta et al^[14] revealed almost the same incidence rate of about 57% in T2DM. Lin et al reported that the prevalence of CAN was higher in T2DM than control group.

In our study the cardiac parasympathetic damage occurred early in diabetes group followed by sympathetic damage. Similar report was stated by Ewing, Talman, Bennett, Wheleers and Watkin et al.^[16] They suggested the possible reason for earlier parasympathetic damage is either due to wide spread function of autonomic nervous system hang on vagal activity or heart rate test are more sensitive than blood pressure test. And also they suggested that the longest fiber of sympathetic nerve is preserved from axonal degeneration. But a slight conflickion by Ninkovic V, Ninkovic S and Zivojinovic D.^[17] stated that the same pattern of damage was occurred for parasympathetic and sympathetic nerve with the course of diabetes.

Pathogenesis of CAN is multi-factorial. Uncontrolled blood sugar level causes direct damage of the neuron or reduced blood flow to the nerve by activating the polyol pathway which accumulates the sorbitol and probably changes the NAD: NADH ratio.

Protein kinase C is activated which causes vasoconstriction which decreases neuronal blood flow. Raised level of oxidative stress with more production of free radicals is the reason for damage the vascular endothelial cells and decreases the NO₂ bioavailability leads to vasoconstriction. However, increases production of nitric oxide causes nitrosative stress due to the excess formation of peroxynitrite which damage the endothelium and neurons. Decreases endoneurial blood flow and reduced oxygen level in nerve (Nerve hypoxia) is occurred due to formation of advanced glycosylation end product and lack of essential fatty acid, and decreased neurotrophic growth factors (mainly in the endoneurial blood vessels) which alter the nerve function. As the consequence of this multi- factorial process might activated the poly ADP ribosylation process leads to reduction of ATP causes cell necrosis and also stimulate the gene which could involved in neuronal damage.^[18-27]

In our study we observed the higher incidence rate of CAN was seen in T2DM with GERD group when compared with T2DM group. Severity of autonomic dysfunction was more in diabetes mellitus with GERD group than diabetes mellitus group. Benefits of AIMS AFT LAB criteria are to find out the autonomic neuropathy on both sympathetic and parasympathetic division of autonomic nervous system. In our study, based on this classification the severity of parasympathetic and sympathetic was progressively increased in type 2 Diabetes mellitus with and without GERD group. Further the damage of parasympathetic nerve was affected earlier than the sympathetic nerve damage.

Thus our study clearly showed that the severity, staging and degree of autonomic dysfunction increases when the complication of increases with diabetes increases which leads to more prone for cardiovascular problems.

CONCLUSION

Thus we concluded that we have highly recommended the clinician to check the degree and severity of cardiovascular autonomic neuropathy in diabetes patients with and without GERD by a simple non-invasive technique Ewing's cardiovascular autonomic function test for the betterment of patient's life.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

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