Electrocardiographic Abnormalities and Cardiac Autonomic Neuropathy In Type 2 Diabetes Mellitus Patients

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Abstract: Background and Objectives**:** As Cardiac Autonomic Neuropathy (CAN) in Type 2 Diabetes Mellitus patients is implicated in arrhythmogenesis and sudden cardiac death; we aimed to determine the prevalence of Cardiac Autonomic Neuropathy and to compare the mean CAN scores of those patients with and without electrocardiographic abnormalities. Methodology**:** After a detailed history and clinical examination, 100 diabetic patients were subjected to Ewing's and Clark's cardiac autonomic function tests. CAN scores were computed and their electrocardiograms (ECGs) were studied. Results**:** 72% had severe CAN (CAN score ≥ 5). 76% had abnormal ECGs with mean CAN scores being higher in those with abnormal ECGs (Mean=7.0 ± 1.7 vs 4.3 ± 1.2, p<0.001). Significant associations were found between CAN scores and age (p=0.013), peripheral neuropathy (p=0.04) and symptoms of dysautonomia (p=0.03). There was a significant difference between the mean CAN scores of those with Coronary Artery Disease (CAD) when compared to those without CAD (Mean 7.26 ± 0.57 vs 6.12 ± 1.93, p=0.012) and between those with longer compared to shorter duration of diabetes(Mean 6.9±1.8 Vs 5.7±1.9, p=0.002). Interpretation and Conclusions**:** Diabetics with abnormal ECGs, CAD and longer duration of diabetes had higher mean CAN scores. As this complex inter-relationship between Diabetes, CAN & CAD can cause abnormalities in heart rate control, a high index of suspicion for asymptomatic cardiovascular disease is needed in diabetics. [Sindhuja K NJIRM 2015; 6(5):38-45]

Key Words: Cardiac autonomic neuropathy, CAN score, Diabetes Mellitus, ECG.

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Introduction: Diabetes Mellitus (DM) affects 347 million people worldwide[1] and 62.4 million are affected in India [2]. Type 2 Diabetes comprises 90% of people with diabetes around the world, and is largely the result of excess body weight and physical inactivity. Diabetic neuropathies, including Cardiac Autonomic Neuropathy (CAN) are chronic complications of Type 2 DM, conferring high morbidity and mortality[3]. Implications of autonomic dysfunction (dysautonomia) are the most overlooked of all complications, while sensory and motor neuropathies have received a larger share of attention[4]. It manifests in the heart as CAN. Diabetes has been established as a coronary risk equivalent[5]. Coronary Artery Disease (CAD) in diabetics may be diagnosed only very late, such as, when it manifests in an acute setting as Myocardial Infarction or Unstable Angina. It may remain dwelling asymptomatically for years together. CAD in turn may trigger disorders of rhythm. Underlying CAN may increment the role of CAD in arrhythmogenesis[6]. The underlying risk factors for an arrhythmogenic substrate in patients with diabetes mellitus include regional myocardial autonomic denervation, silent ischemia, slowed conduction, heterogeneities in atrial and ventricular repolarisation, extent of myocardial damage and scar formation and spontaneous calcium release from sarcoplasmic reticulum due to activation of CaMKII dependent pathway[6-8]. Advanced stages of CAN, in addition to lowering heart rate variability, produce changes in ventricular repolarization thereby manifesting as ECG changes[9]. QT prolongation in patients with Cardiac Autonomic Neuropathy (CAN) may also predispose individuals to life-threatening cardiac arrhythmias and sudden death[10].

There is an independent role of CAN, synergistic with perfusion defects, in predicting cardiac events and hence contributing to ECG abnormalities in DM patients[11]. ECG abnormalities in turn can predict the occurrence of a future cardiovascular event more accurately than risk factors alone[12]. CAN can be detected clinically by Ewing and Clark's Autonomic Function Tests which can be performed by the bedside of the patient[13]. A simple scoring system developed by Bellavere et al is applied to the results to quantify CAN (CAN score)[14]. It is necessary to establish the prevalence of these

conditions in the general population, more so in a country like India where in an urban corporate hospital, diabetes and CAD may be treated independently by exclusive specialists, and the link may be unapparent on a superficial level. Diagnosis of dysautonomia may have further non-cardiac implications like erectile dysfunction, gastroparesis and obstructive sleep apnea which may warrant further interventions to improve the quality of life[15].

We were therefore interested in evaluating the types of ECG findings prevalent in diabetics, due to the aforementioned pathophysiological mechanisms revealed by various researchers, in our setting. Hence, we aimed to bring to light any findings suggestive of relationship between CAN scores and variables like ECG findings, age, symptoms of dysautonomia, duration and severity of diabetes and prevalence of co-morbidities to fill in the lacunae and streamline the theoretical evidence to our context.

The objectives of this study were to

1. Determine the different ECG abnormalities in diabetics and the prevalence of Cardiac Autonomic Neuropathy.
2. Compare the mean CAN scores in diabetics with and without ECG abnormalities, in those with and without Coronary Artery Disease and in those with varying duration of diabetes.
3. Determine the association between CAN scores and age, duration of diabetes, co-morbid conditions and symptoms of dysautonomia in diabetic patients.

Material and Methods: This study was conducted on 100 patients of Type 2 Diabetes Mellitus aged 18 - 75 years who presented to Sri Muthukumaran Medical College Hospital & Research Institute in the period May-July 2014 irrespective of duration of diabetes or treatment status and who gave their written informed consent. Institutional Ethics Committee clearance was obtained prior to the beginning of this study. Subjects who were on prescription drugs which could influence the conduction system of the heart and the autonomic nervous system like beta blockers, other anti arrhythmic drugs, those with acute or chronic electrolyte disturbances, those with acute cerebro-vascular disease, pregnant women, patients suffering from malignancies, patients who were very sick and unable to take part in the study were excluded.

A detailed history was elicited from every participant, who then underwent a thorough medical examination and the findings were recorded. Specific questions regarding symptoms suggestive of autonomic dysfunction and arrhythmias were posed to the participants like those related to gustatory sweating, enteropathy, cystopathy, orthostatic hypotension and their answers were recorded. All study participants underwent relevant blood investigations and ECG. The ECG was interpreted for the presence of any arrhythmia or conduction abnormality or ischemic changes by the physician. All participants underwent a bedside testing of cardio-vascular reflexes (Ewing's And Clark's)[13] for Cardiac autonomic dysfunction.

The participants were subjected to

1. Deep Breathing: The participants were asked to do deep breathing for one minute at 6 breaths per minute with five seconds for inspiration and five seconds for expiration. The heart rate (HR) in beats per minute was calculated during each cycle of inspiration and expiration. The mean value of difference in heart rate during inspiration and expiration (Maximum HR-Minimum HR) was calculated[13] .
2. Valsalva Maneuver: The participants were asked to exhale forcibly into the mouthpiece of a manometer at 40 mm Hg for 7 to 15 seconds. The ratio of minimum heart rate after the maneuver and maximum heart rate during the maneuver was recorded as the Valsalva ratio[13] .
3. Response To Standing: After getting the basal resting heart rate, the participant was asked to stand up from supine position. Heart rate was measured for one whole minute. 30^{th} second and 15^{th} second heart rate after standing was used to calculate the 30:15 ratio[13] .
4. Response to sustained Hand Grip: Blood Pressure (BP) recording was done in the resting posture. Next, they were asked to squeeze a pliable article (a partially inflated BP cuff) to establish their maximum force. Then they were asked to squeeze at 30% of their maximum force. BP was recorded on the

contra-lateral arm. The difference in systolic blood pressures was calculated[13].

5. BP Response to Standing: BP was recorded with the participant lying supine. Then after 2 minutes, they were made to stand up and BP was recorded. The difference in systolic blood pressures was calculated[13].

The findings of the autonomic function tests were interpreted on the basis of the scoring system for CAN developed by Bellavere et al [14] . Data analysis was done with the help of statistical software IBM-SPSS Statistics-20. The continuous variables were analyzed and interpreted by Student's 't' test. The categorical variables were analyzed and interpreted by Chi Square Test (χ^2).The p values less than 0.05 were considered as significant.

Scoring of Cardiac Autonomic Function Tests (Ewing And Clark's) [13]

SCORE	PULSE RATE VARIATION			BLOOD PRESSURE VARIATION	
	Deep Breathing	Valsalva Ratio	Response to Standing	Response to Hand grip	Response to Standing
0	>15	> 1.20	> 15	> 15	≤ 10
1	11 – 15	1.11 – 1.20	12 – 15	11 – 15	11 - 29
2	≤ 10	≤ 1.10	< 12	≤ 10	30

Interpretation of total scores [14] : The scores were interpreted as follows
0 - 2: normal,
3 - 4: Borderline CAN and
≥ 5: Severe CAN

Results: The mean age of the participants in this study was 56.5±11.08. The proportion of participants over the age of 60 years was 42%. The male to female ratio was 1:1.32. The mean duration of affliction with diabetes was 6.95 ± 5.9 years. 55% of them were only on oral anti-diabetic medications while the rest were on a combination of Insulin injections with oral hypoglycaemic agents.

66% of the participants reported symptoms of dysautonomia when questioned. 46% of them had evidence of microvascular complications with 20% of them having diabetic foot syndrome, 18% having peripheral neuropathy and 8% having nephropathy. 39% had Systemic Hypertension, 19% of them had coexisting CAD while 18% of them had dyslipidemia.

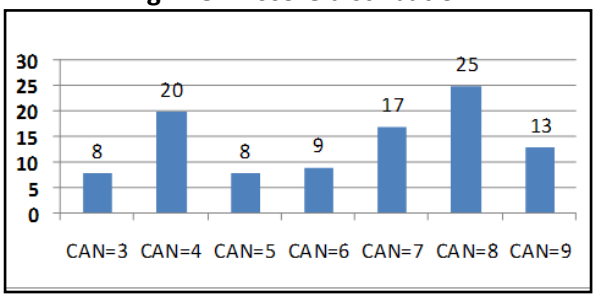
76% of our participants had an abnormal ECG. 36% of them had more than one finding on the ECG. The arrhythmias, conduction disturbances and other findings recorded on ECG are tabulated in **Table 1.**

Table 1: Percentage distribution of various arrhythmias, conduction abnormalities and other ECG abnormalities.

Arrhythmia/conduction abnormality	Percentage (n=100)
Sinus tachycardia	23
Sinus Bradycardia	16
Right bundle branch block	15
Left bundle branch Block	6
Prolonged QT interval	4
Other arrhythmias/Intra-Ventricular conduction defects	10
Other ECG Findings: Ischemic changes	27
Left/right Axis deviation	9
Ventricular hypertrophy	7
Atrial enlargement	4

All the participants had an element of Cardiac Autonomic Neuropathy. The mean CAN score of the population was 6.3 ± 2.0. 72% had severe Cardiac Autonomic Neuropathy with CAN scores ≥5. **Figure 1** depicts the CAN score distribution.

Fig 1: CAN score distribution



The mean CAN score in participants having an abnormal ECG was higher than those with normal ECG, the difference achieving statistical significance. The association between Sinus bradycardia and CAN scores ≥ 5 was also found to be statistically significant. The mean CAN scores in those with CAD was higher than those without CAD, the difference being significant. The mean CAN scores in diabetics with more than 5 years duration was higher than those with a lesser

duration of the disease, the difference achieving statistical significance **(Table 2).**

Table 2: Comparison of Mean CAN Scores based on ECG findings, CAD and duration of diabetes.

	ECG		CAD**		Duration	
	Normal ECG (n=24)	Ab-normal ECG (n=76)	Absent CAD (n=81)	Present CAD (n=19)	<5 years (n=48)	>5 years (n=52)
Mean CAN * Scores	4.3 ± 1.2	7.0 ± 1.7	6.12 ± 1.93	7.26 ± 0.57	5.7 ± 1.9	6.9 ± 1.8
Difference in Means	2.7		1.14		1.2	
Student's t value	6.987		3.232		2.5	
Significance	p <0.001		p =0.012		p =0.002	

CAN * = Cardiac Autonomic Neuropathy CAD**= Coronary artery disease

There was a significant association between age and CAN scores. The presence of a diabetic peripheral neuropathy was associated with higher mean CAN scores than those without. The association between symptoms of dysautonomia and CAN scores > 5 was found to be statistically significant **(Table 3).**

Table 3: Association between Severe CAN and age, diabetic peripheral neuropathy and symptoms of autonomic dysfuction.

Mean CAN* SCORE	Age (years)		Diabetic peripheral Neuropathy		Autonomic dysfunction		Total
	< 60	≥ 60	No	Yes	Asymptomatic	Symptomatic	
<5	21	7	27	1	14	14	28
≥5	37	35	55	17	20	52	72
Total	58	42	82	18	34	66	100
χ^2	4.614		4.211		4.43		
Significance	p=0.013		p=0.040		p=0.03		

CAN * = Cardiac Autonomic Neuropathy

Discussion: This cross sectional study points out that there were higher CAN scores in subjects having abnormal ECG findings. This is in conformity with another study carried out by Prabhakar Rao et al in which ECG changes correlated positively with the degree of cardiac autonomic neuropathy[16]. According to a follow up study done by Ana de Santiago et al, the presence of a baseline ECG abnormality was an independent predictor of future cardiovascular event with a relative risk of 5.45 in diabetics without a known cardiovascular disease[12]. A similar follow up study demonstrates that repolarization abnormalities like ST depression were a predictor of cardiovascular morbidity in diabetic American Indians[9].

72% of our subjects had severe CAN and the mean CAN score was 6.3±2.0. This is consistent with various studies which report a prevalence ranging from 40% to 80%.However Ewing et al back in 1982, have reported a lesser prevalence (20%-40%)[17]. A study done by Xueli et al reported prevalence as high as 80%[18]. There are variations in prevalence rates of CAN in different studies as there are differences in selection criteria in terms of inclusion of subjects with co-morbidities, with and without complications of Diabetes, subjects with newly diagnosed DM and those having varying periods of affliction, patients on regular treatment as opposed those with irregular medications or those exercising only diet control.

In our study, the mean CAN scores of subjects with CAD were higher than those without CAD. As CAD and Diabetes represent the same pathophysiological risk profile for the coronary endothelium and atherosclerosis, this result is foreseeable. Hence, increase in the prevalence of diabetes indirectly implicates an escalating risk of CAD as well. According to a study by Haffner et al, diabetics are known to have a two to four times increased CAD risk, and CAD has been reported to occur two to three decades earlier in diabetic subjects as opposed to their non-diabetic counterparts [19]. However, there was no significant association between presence of other co-morbidities and CAN.

Sinus tachycardia and bradycardia were found in 23% and 16% of our diabetic subjects respectively. Krishna et al found that sinus tachycardia and sinus bradycardia were present in 38% and 10% of the subjects respectively[20]. This is probably explained by the unopposed sympathetic activity or augmented sympathetic drive stemming from parasympathetic-sympathetic dyssynergia in many diabetics with CAN[21]. Imaging of myocardial sympathetic innervation with various radiotracers (eg, MIBG) has shown that predisposition to arrhythmias and an association with mortality may also be related to intracardiac sympathetic imbalance[21]. In another study done by Malone et al on streptozotocin induced diabetic rats, the study animals also developed bradycardia[22].

The presence of Sinus bradycardia was associated with the presence of severe cardiac autonomic neuropathy (CAN scores≥5) in our study. Right Bundle Branch blocks were found in 15% of our subjects. Movahed et al, in his review has concluded that there are many non randomized studies reporting right bundle branch block (RBBB), bifascicular block and high degree atrioventricular (AV)-block but not left bundle branch block (LBBB), in diabetic patients [6]. According to the review, autonomic neuropathy, diabetes induced cardiovascular disease and silent Myocadial Infarction could possibly be implicated in the pathogenesis of RBBB, bifascicular block and higher degree AV block. Diabetic patients with concomitant LBBB have more severe and extensive CAD and advanced left ventricular dysfunction compared with those diabetics without LBBB and those with isolated LBBB [23]. Higher degree AV blocks, and complete heart block were found in 10% of our subjects. Likewise, Krishna et al found complete heart blocks in 12% of their subjects [20].

There was one subject with Sick Sinus Syndrome, a 60 year old man, with hypertension as the co-morbidity, who had CAN score of 9. There has been an established association of sick sinus syndrome and hyperinsulinemia and insulin resistance due to diabetes. This may be because of malfunction of sinus node automaticity due to chronic exposure of insulin which is key regulator of Na^+K^+ATPase pump present on the membranes[24]. Prolonged P-R interval (First degree heart block) was found in a female subject aged 56 with poorly controlled diabetes for five years which had also led on to diabetic foot. First degree heart block was also reported in two subjects in the study done by Krishna et al [20].

Ischemic changes were the most prevalent ECG finding in our study (27%). Resting ECG abnormalities was suggestive of asymptomatic ischemic heart disease in diabetics as found out by a follow up study done using interpretation of ECG according to the Minnesota Code[25]. Hence, Diabetic Cardiomyopathy can lead to cardiac dysfunction without any evidence of ischemic, hypertensive and valvular heart disease[26].

There was a significant association between age and severity of CAN. This is consistent with a study carried out by Kuroda et al in which it was concluded that autonomic nerve function is related to age by analyzing cardiac beat to beat variation during deep breathing[27]. However, most of the subjects below the age of 60 in our study also had CAN scores ≥ 5(37 subjects)**.** This requires further elucidation as Indian patients may have the onset of autonomic dysfunction at an earlier age.

The mean CAN scores were higher in subjects whose duration of diabetes was > 5years than those with lesser duration. This is similar to the results of a study done by Valensi et al, where presence of moderate or severe CAN correlated positively with the duration of diabetes[28]. In a study done by Nayak et al using similar scoring system and bedside tests of autonomic function, duration of diabetes greater than 6 years was associated with higher mean CAN scores[29].

There was significant association between presence of symptoms of autonomic dysfunction and high CAN scores. Giddiness on standing and palpitations were the most frequently encountered symptoms (35% and 24% respectively) in our study. This observation is consistent with studies done by Basu et al and Nayak et al[29,30] where postural dizziness was encountered in 36% and 44% of their subjects respectively.

Fasting and postprandial blood sugars were not associated with severity of CAN in our study. This is plausible as they are not true indicators of long term glycemic control. Nayak et al reported a strong positive correlation between the level of glycemic control in terms of HbA1C levels and CAN[29]. Similar to our study, Nayak et al have also reported higher mean CAN scores in those with diabetic peripheral neuropathy[29].

Stella et al, concluded that in diabetes, CAN is ultimately the result of complex interactions among the degree of glycemic control, disease duration, age-related neuronal attrition, and systolic and diastolic blood pressure[31]. Also, Ana de Santiago et al have concluded that ECG would be a cheap, immediate tool to detect diabetics with a higher risk of future cardiovascular events[12].The results of our study also seem to be reflecting such conclusions.

There is a potential for the reversal of CAN. Early detection of autonomic dysfunction allows time for intervention by the physicians, to improve metabolic control and to use therapies such as ACE inhibitors and β-blockers which have proven to be effective for patients with CAN[15]. Aldose reductase inhibitors have also been shown to be useful in preventing the progression of complications of cardiac autonomic neuropathy in some cases though they have shown no appreciable effect on glycemic control[3,15]. Trimetazidine and aminoguanidine have cytoprotective effect and have emerged as therapy for "Diabetic cardiopathies"[32].

The limitations of this study are, with regard to the fact that majority of the subjects consented were in a hospitalized set-up. Other methodologies involving ample resources like usage of ECG recordings from Holter Monitors and spectral analysis of Heart Rate Variability may be required to conclusively point out that CAN may set the ground for arrhythmias and conduction abnormalities. Follow up studies are required to determine the predictive value of ECG abnormalities in determining the occurrence of cardiovascular events. Larger sample size and regression analysis are required in order to find out the independent causal relationship between each of the ECG findings and CAN scores and to delineate the cause-effect relationship of each risk factor and co-morbidity.

Conclusion: In conclusion, the results of our study are suggestive that abnormal ECG findings may be a manifestation of progressive and severe cardiac autonomic neuropathy (high CAN scores). Severity of CAN is found to increase with advancing age and hence age is an important factor to be considered to decide upon the screening intervals. Co-morbid conditions like CAD and complications of diabetes like peripheral neuropathy, are associated with concomitant presence of severe cardiac autonomic dysfunction. High prevalence rates of severe CAN with increasing duration indicates that caution should be exercised in such cases, where patients may be predisposed to silent ischemia and undetected arrhythmias. Although there is significant association between presence of symptoms and high CAN scores, patients without overt diabetic complications need not necessarily have normal autonomic function. Hence CAN scoring may be correlated with ECG interpretation order to identify diabetics with potential risk of cardiovascular disease.

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