Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL 13, ISSUE 08, 2022

Original Research Article

A Study on Cardioautonomic Dysfunction in Type 2 Diabetes Patients in a Tertiary Care Hospital, Mysore with Special Reference to QT Ratio

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Received:08/05/22 Revised:23/09/22 Accepted:19/11/22

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Abstract

Background and Objectives: Cardiac autonomic neuropathy (CAN) encompasses damage to the autonomic nerve fibres that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics. The reported prevalence of CAN varies depending on the clinical setting, type and number of tests performed, different diagnostic methods applied, and selection criteria for the patients. Studies using different end points have reported prevalence estimates ranging from 1% to 90%. Hence we studied CAN in T2DM patients and attempted to see the correlation between the two along with glycaemic control and QT ratio in CAN.

Materials and Methods: The study was conducted on 100 type2 diabetes subjects meeting inclusion and exclusion criteria. Subjects were tested for five cardiac autonomic neuropathy tests, HbA1c levels and ECG with reference to QT ratio.

Results: In our study 60% were asymptomatic and 40% were symptomatic for diabetic autonomic neuropathy(DAN) symptoms. 32% of asymptomatic DAN patients had early CAN. Patients who had absent, early and definite CAN were 28%, 44% and 28% respectively. Majority of patients in absent CAN group (15%) were having DM less than 5yr duration. In definite CAN group (20%) were having above 10yr duration. Stages of CAN is directly associated with duration of diabetes which is statistically significant (P value: <0.001). Among 28 patients who had definite CAN, corrected QTc was prolonged in 22 patients.

Conclusion: 32% of asymptomatic DAN patients had early CAN. Poorly controlled diabetic state group had CAN in 82% of the subjects concluding that stages of CAN is directly related to the duration of diabetes. QTc dispersion was significantly high in diabetics with autonomic neuropathy.

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Keywords: Cardiac autonomic neuropathy, diabetic autonomic neuropathy, QTc, type2 diabetes mellitus.

Introduction

Diabetes is a group of metabolic diseases which has become pandemic, rapidly spreading among the population. It is characterized by chronic hyperglycemia with disturbances of carbohydrates, protein and fat metabolism which leads to defects in insulin secretion, insulin action or both[1]. Several pathogenic pathways are involved in development of diabetes. The metabolic dysregulation associated with DM leads to secondary physiological changes in multiple organ systems, which are mainly associated with high morbidity and has a tremendous burden, if they are not treated timely and adequately. The reports of WHO says that the total diabetics in India in 2000 were 31.7million and is predicted to afflict up to 79.4 millions by 2030[2]. A significant portion of individuals with DM are undiagnosed. Diabetes complications can be divided mainly into Vascular and non vascular. Vascular complications have been further divided into microvascular (retinopathy, neuropathy, nephropathy) and macrovascular (coronary heart disease , peripheral artery disease and cerebrovascular disease)[11]. Among them, cardiovascular disease is one of the most common complication that increase mortality in these individuals. CAN is a common form of diabetic autonomic neuropathy which encompasses damage to the autonomic nerve fibres that innervate the heart and blood vessels leading to abnormalities in heart rate control as well as peripheral and central vascular dynamics. CAN is one of cause of morbidity and mortality which is associated with a high risk of cardiac arrhythmias and sudden death. CAN is associated with a poor prognosis and may result in postural hypotension, exercise intolerance, enhanced intraoperative instability. It is likely that dysfunction of ANS is underdiagnosed cause of excessive morbidity and mortality in adults with Diabetes & with increased duration of disease, poor glycaemic control and in presence of various risk factors abnormality further worsens. Autonomic dysfunction is common in diabetics but symptomatic autonomic neuropathy is not common hence recognition and treatment of autonomic neuropathy may improve symptoms, reduce squeal and improve quality of life. The study is aimed to find out relation of corrected QT(QT_c) interval and QT_c dispersion with diabetic cardiac autonomic neuropathy in type 2 DM so that we can identify high risk patients for sudden cardiac death.

Materials and Methods

Source of data:

Inpatients admitted in Department of General Medicine, K R Hospital Mysore

Method of collection of data (including sampling procedure, if any):

Sample Size: 100

Calculated with level of significance(α) 5% & absolute allowable error(d) 8% with prevalence of Cardioautonomic neuropathy among diabetes is 81%[5]

Study population: Type 2 DM admitted to the hospital during study period

Type of study: cross sectional study

Study Period: June 2020-July 2021

Sampling method: Purposive sampling

- All the patients were evaluated by detailed history including classical symptoms of autonomic neuropathy, physical examination and blood investigations after taking a well informed consent.
- A group of five autonomic function tests will be done

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1. Orthostatic Blood Pressure recordings
2. Diastolic blood pressure response to isometric exercise
3. Heart rate response to Valsalva manoeuvre
4. Heart rate variation to Deep Breathing (E:I Ratio)
5. Heart rate response to standing

   Autonomic dysfunction when present was classified as normal, early, definite, and severe using a modification of the criteria of Ewing and Clarke[12] as follows,

   1. absent: all five tests normal.
   2. Early involvement: one of the three heart rate tests abnormal
   3. Definite involvement: two or more of the heart rate tests abnormal

- A 12 lead ECG will be taken and RR interval , heart rate , QT_c interval and QT_c dispersion will be calculated
- $QT_c = QT/\sqrt{RR}$
- QT_d = longest QT_c - shortest QT_c

Method of collection of data:

All patients who fulfil the inclusion and exclusion criteria and are admitted to K R Hospital during the study period.

- **Inclusion criteria:**1) T2DM Patients
- **Exclusion criteria:**
  a) Known Cardiac Diseases
  b) Chronic Kidney Disease
  c) On Drug therapy influencing autonomic functions and QT interval
  d) Hypokalemia
  e) Hypomagnesemia
  f) Hypocalcemia

Statistical Analysis:

Appropriate statistical methods will be used to compute frequency tables and proportions. In order to study various associated factors Chi square test will be applied and significance of the factors will be tested at 5% level of significance.

Results

Table 1 : Age distribution of the study participants. [n=100]

Age Distribution	**Frequencies**	**Percentages**
31-40 years	5	5
41-50 years	33	33
51-60 years	62	62
Total	**100**	**100**
Mean Age of the study participants*: 50.83 ± 5.47		

*Mean ± Standard Deviation

In our Study, Among 100 patients mean age of study population was 50.83 ± 5.47 years

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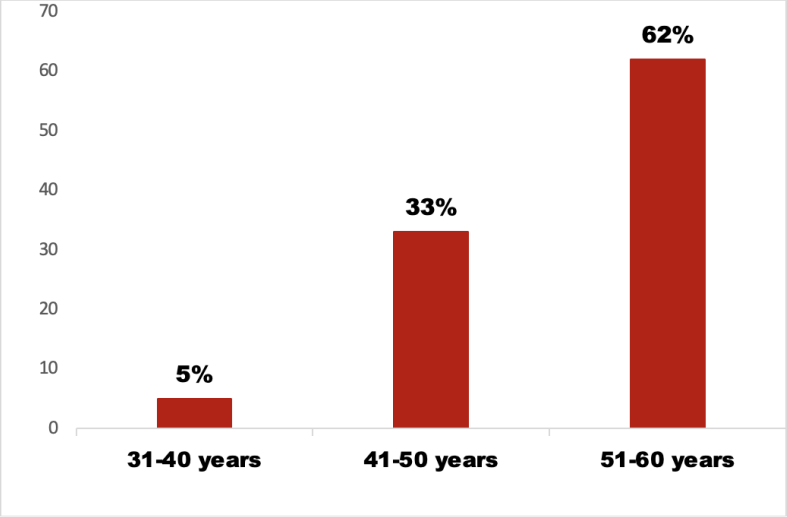

Figure 1: Age distribution of the study participants

Table 2: Gender distribution of the study participants. [n=100]

Gender	Frequencies	Percentages
Male	51	51
Female	49	49
Total	**100**	**100**

Among 100 patients, 51 patients were male and remaining 49 were female.

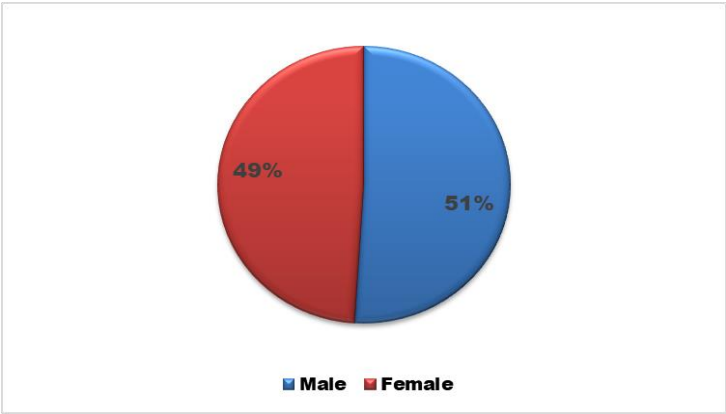

Figure 2: Gender distribution of the study participants

Table 3: Body mass index categorisation of the study participants. [n=100]

Body mass index categorisation*	Frequencies	Percentages
Normal(18.5-22.9)	14	14
Overweight(23-24.9)	26	26
Obese (>25)	60	60
Total	**100**	**100**

*Body mass index classification according to the WHO Asia Pacific cut-offs.

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In our study, 60% of Patients were BMI of above 25 and 26% of patients were overweight (BMI 23-24.9)

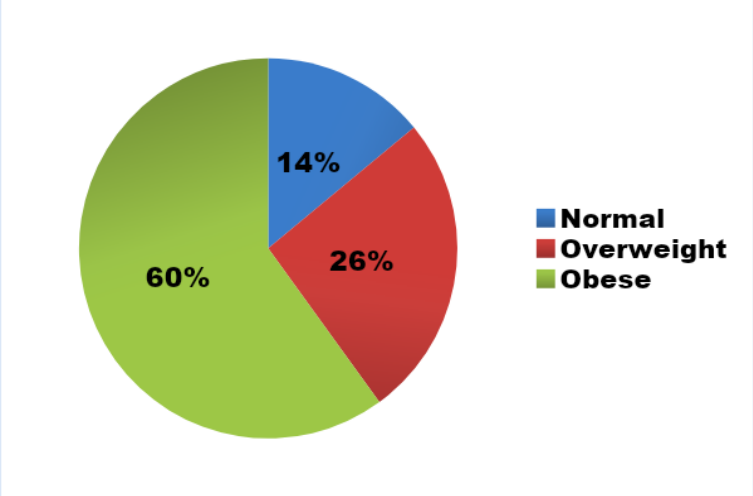

Figure 3 : Body mass index categorisation of the study participants

Table 4: Classification of study participants according to the Duration of Diabetes Mellitus . [n=100]

Duration of Diabetes Mellitus	Frequencies	Percentages
<5 years	25	25
5-10 years	45	45
>10 years	30	30
Total	**100**	**100**

In our study, 45 % of study population had duration of Diabetes for 5-10 years and 30% had duration more than 10 years .

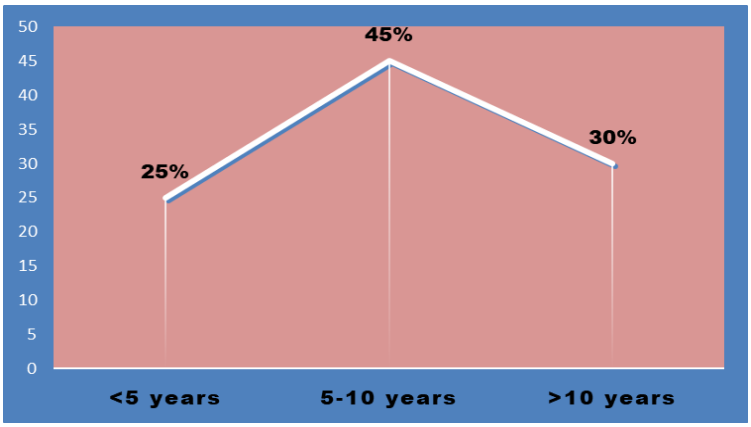

Figure 4: Classification of study participants according to the Duration of Diabetes Mellitus.

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Table 5: Prevalence of Cardio-Autonomic Neuropathy [CAN] among the study participants [n=100]

Cardio-Autonomic Neuropathy [CAN]	Frequencies	Percentages
Early	44	44
Definite	28	28
Absent	28	28
Total	**100**	**100**

In our study, 28% were having definite CAN , 28% were not having CAN & 44% of patients had Early CAN.

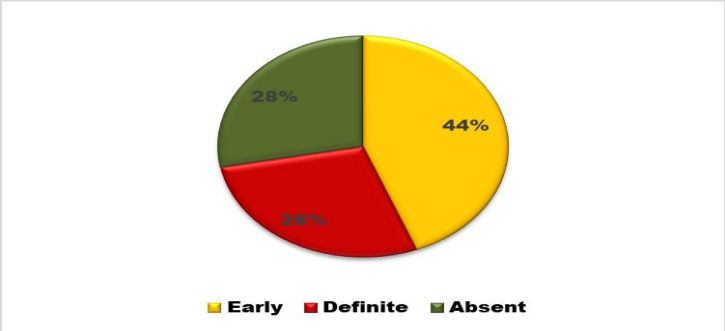

Figure 5: Prevalence of Cardio-Autonomic Neuropathy [CAN] among the study participants

Table 6: Prevalence of Diabetic-Autonomic Neuropathy [DAN] Symptoms among the study participants . [n=100]

DAN symptoms	Frequencies	Percentages
Present	40	40
Absent	60	60
Total	**100**	**100**

In our study, 40% were symptomatic and 60% were asymptomatic for diabetic autonomic neuropathy symptoms .

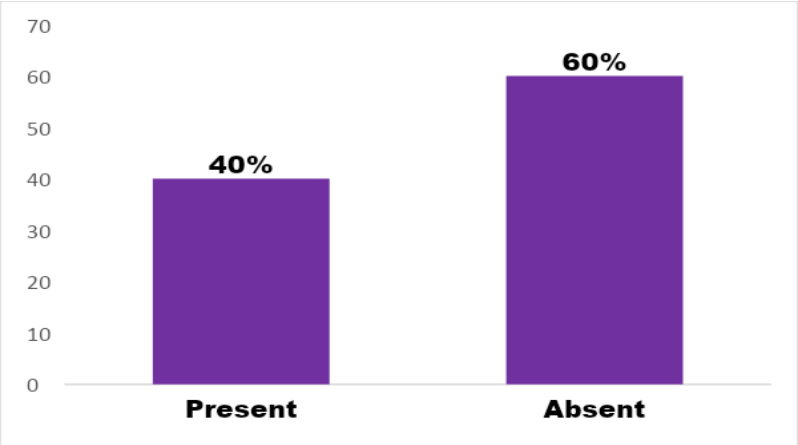

Figure 6: Prevalence of Diabetic-Autonomic Neuropathy [DAN] Symptoms among the study participants

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Table 7: QTc Interval among the study participants . [n=100]

QTc Interval [milli-seconds]	Frequencies	Percentages
<440	56	56
>440	44	44
Total	**100**	**100**

In our study, QTc interval was >440ms in 44% of the study subjects and <440 ms in 56%.

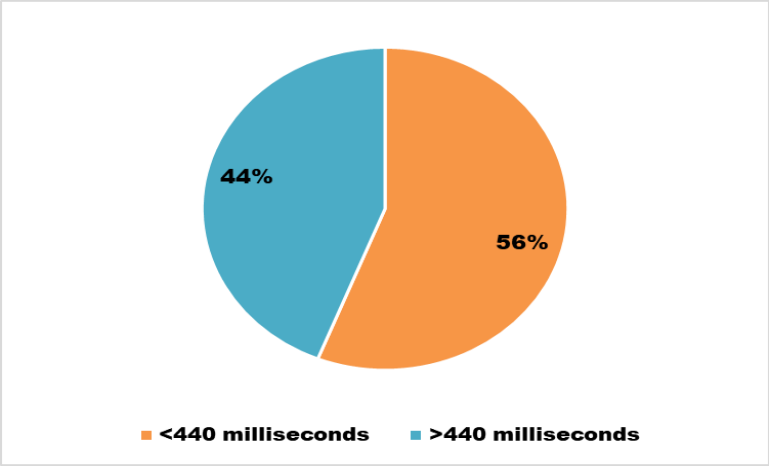

Figure 7: QTc Interval among the study participants.

Table 8 : Association between Age and Cardio-Autonomic Neuropathy . [n=100]

		Cardio-Autonomic Neuropathy		
		Early	Definite	Absent
Age	31-40 years	2	1	2
	41-50 years	11	13	9
	51-60 years	31	14	17

In our study , the prevalence of definite CAN was highest in 51-60 years and Early CAN was highest in 51-60 years.

Table 9 : Association between Duration of Diabetes Mellitus and Cardio-Autonomic Neuropathy . [n=100]

		Cardio-Autonomic Neuropathy		
		Early	Definite	Absent
Duration of Diabetes Mellitus	<5 years	8	2	15
	5-10 years	27	6	12
	>10 years	9	20	1

In our study, 28% of study population were not having CAN , 28% and 44% were having definite and early CAN respectively . In Definite CAN group majority had duration of DM of more than 10 years (statistically significant p<0.00001)

Table 10 : Association between Duration of Diabetes Mellitus and Cardio-Autonomic Neuropathy . [n=100]

		Cardio-Autonomic Neuropathy		
		Early	Definite	Absent
Duration of Diabetes Mellitus	<5 years	8	2	15
	5-10 years	27	6	12
	>10 years	9	20	1

In our study, 28% of study population were not having CAN, 28% and 44% were having definite and early CAN respectively. In Definite CAN group majority had duration of DM of more than 10 years (statistically significant p<0.00001)

Table 11: Association between QTc Interval and Cardio-Autonomic Neuropathy . [n=100]

		Cardio-Autonomic Neuropathy		
		Early	Definite	Absent
QTc Interval	<440 msec	27	6	23
	>440 msec	17	22	5

From the table ,QTc interval prolongation occurs with development of CAN . Prolongation of QTc is correlated with Cardiac Autonomic neuropathy (p value <0.0001)

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Discussion

The results of this study illustrate the fact that Cardiac autonomic dysfunction is common in diabetic patients and its prevalence increases with duration of diabetes. Similar results have been reported in previous studies conducted in various parts of India and other countries[4-7.] The sample size in our study is 100 patients. We sub grouped our diabetic patients into duration of <5 years, 5-10 years and >10 years to evaluate the impact of duration of diabetes and prevalence of cardiac autonomic neuropathy.

Mohan et al studied the prevalence of CAN in 336 patients with Type 2 Diabetes mellitus in southern part of India, and there was an increase in prevalence of CAN with increase in duration of Diabetes[6]. In our study, the prevalence of CAN was found to be 40 % among 0-5 years group, of which 32% had early CAN and 8% had definite CAN.

In a study done by Toyry J P et al[8] on clinical significance of autonomic neuropathy in Type 2 DM, a total of 113 patients with newly diagnosed type 2 diabetes and 144 control subjects were examined at baseline and after 5 and 10 years of follow up. The frequency of autonomic dysfunction at baseline , 5 & 10 years was 4.9% ,19.6% and 65% respectively[4] . In our study the prevalence of definite CAN at <5yrs, 5-10yrs and >10yrs were 8 % ,40% and 66 % respectively. Pappachan J M et al studied the prevalence of the CAN among Type 1 & 2 DM in south India, assessed by the five autonomic function tests by Ewing's methodology. The prevalence of CAN was 60%[3] which is comparable to the results obtained in this study(72%).

In a study conducted by Vinik et al, it was found that parasympathetic damage takes place earlier than sympathetic damage in diabetic cardiovascular autonomic neuropathy[7.] The parasympathetic system can be assessed by autonomic tests which include heart rate variability (HRV) to deep breath, valsalva & Blood pressure tests. In our study, almost everyone with early CAN had abnormal HRV which emphasizes the importance of HRV testing as screening modality for early autonomic dysfunction in diabetes.

In our study, patients who had definite CAN, majority of them had symptoms of autonomic dysfunction. Chen H S et [9] al determined 8 year survival rate for patients with abnormal cardiovascular reflex(CVR) tests, which was 76.4% in females and 63.6% in males, compared with 80.9 and 93.3% for patients with normal cardiovascular reflex tests concluding that patient with abnormal CVR tests may have increased mortality and those combined with postural hypotension may have increased mortality than those without. Abnormal cardiovascular reflex tests may be important predictors of mortality in type 2 Diabetes melitus and however subclinical autonomic dysfunction can be manifested within a year in type 2 diabetes. Early observation by researchers is that near normal glycemic control seems to be the most effective way to delay the onset of CAN and arrest its progression, hence it is necessary to emphasize tight glycemic control for individuals with CAN. Early identification of CAN helps in timely initiation of therapy.

In Electrocardiogram, patients who had definite CAN(28pts), corrected QTc was prolonged in 22(78%), which gives a sensitivity of 78% and specificity of 82% respectively. In this study, comparison of CAN with QTc prolongation was significant.

Pappachan J M [3] et al studied the utility of prolongation of QTc in the ECG to diagnose CAN in patients with diabetes and calculated the sensitivity and specificity of QTc prolongation for the diagnosis of CAN were 77% and 62.5% in type 1 diabetes and 76.5% and 75% in type 2 diabetes respectively. They concluded that QTc interval in ECG can be used to diagnose

CAN with reasonable sensitivity and specificity. The value of sensitivity and specificity for QTc correlates with this study. C P Mathur et al[10] studied patients with diabetes (n=50) with controls (n=20) to understand the relationship between CAN and QTc interval, there were 15(78.94%) cases with QTc prolongation out of 19 diabetics with CAN.

Conclusion

Autonomic neuropathy is not uncommon and it may be a forerunner for the sudden cardiac death, silent myocardial infarction and cerebrovascular accidents. Prevalence of cardiovascular autonomic neuropathy is high in long standing diabetics and increases with duration of diabetes. Its incidence is associated with poor control of diabetes and obesity. QTc dispersion is significantly high in diabetics with autonomic neuropathy. QTc interval in electrocardiogram is a cheap bedside investigation and can be used to diagnose CAN and to identify subset group of people with high risk of sudden cardiac death.

References

1. Bennett, P. H. (2005). Definition, diagnosis, and classification of diabetes and glucose homeostasis. In *Joslin's diabetes mellitus* (14th ed., pp. 332-340). Philadelphia, PA: Lippincott Williams &Willkins.
2. Jayaram B M et al: Type 2 Diabetes Mellitus and its complications: A preventive program, 2008
3. Pappachan J M et al. Cardiac autonomic neuropathy in diabetes mellitus: prevalence, risk factors and utility of corrected QT interval in the ECG for its diagnosis Postgraduate Medical Journal 2008; 84:205-210
4. Doran A and Andrew J B et al. Diabetic Autonomic Neuropathy. The clinical interpretation of improved technology. Diabetes Technology and Therapeutics 2001; 3:77-79
5. Ratzmann K P et al. Prevalence of Peripheral and Autonomic Neuropathy in newly diagnosed Type 2 Diabetes mellitus. J Diabet Complications, 1991; 5: 1-5
6. Mohan V et al. Autonomic Neuropathy in NIDDM and fibrocalculus pancreatic diabetes in south India, Diabet Med 1996; 13: 1038-43
7. Vinik AI, Erbas T: Recognizing and treating diabetic autonomic neuropathy. Cleve Clin J Med 2001; 68:928- 944.
8. Toyry JP, Niskanen LK, Lansimies EA, Partanen KPL, Uusitupa MIJ: Autonomic neuropathy predicts the development of stroke in patients with Non-insulin dependent diabetes mellitus. Stroke 1996; 27:1316–1318.
9. Chen H S et al. Abnormal cardiovascular reflex tests are predictors of mortality in Type 2 diabetes. Diabetic Medicine 2001; 18(4):268-273
10. Mathur et al: QTc Prolongation in Diabetes Mellitus – An Indicator of CardiacAutonomic Neuropathy. Journal, Indian Academy of Clinical Medicine 2006; 7(2): 130-2
11. Longo DL , Fauci AS , Hauser SL et al ,Editors . Harrison's Principles of internal medicine ,19e Newyork , NY :McGraw Hill;2015
12. Ewing Dj, Clarke BF. Diabetic autonomic dysfunction: a clinical view point. In: Dyck PJ, Thomas PK, Asbury AK, Winegrad Al, Porte D jr, eds. Diabetic Dyslunction. Philadelphia: W.B. Saunders Company, 1987: 66-93.