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ACROSS-SECTIONAL STUDY AT A TERTIARY CARE HOSPITAL EVALUATING THE RAPIDITY OF CARDIAC AUTONOMIC NEUROPATHY AND GLYCAEMIC CONTROL IN LONG-STANDING TYPE 2 DIABETES

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ABSTRACT

Background: In addition to increased cardiovascular mortality, malignant arrhythmias, and sudden cardiac death, cardiac autonomic neuropathy is one of the most serious and under-recognized complications associated with long-standing type 2 diabetes mellitus (T2DM). Early detection through standardised Ewing's battery enables therapeutic intervention. Systematic data from Indian tertiary care populations are limited. **Methods:** This cross-sectional study assessed CAN using Ewing's autonomic battery in 200 adults with T2DM of >5 years' duration attending a tertiary care hospital. Five Ewing's tests were performed: Standing blood pressure response to standing, EI ratio to deep breathing, 30:15 ratio to Valsalva, and blood pressure response to sustained hand grip. CAN was defined as ≥2 abnormal tests (early CAN: 1 abnormal; definite CAN: 2–3 abnormal; severe CAN: ≥4 abnormal or ≥2 abnormal with orthostatic hypotension). **Results:** CAN (any, ≥2 abnormal Ewing's tests) was detected in 88 patients (44.0%): early (1 test abnormal) 44 (22.0%), definite CAN (2–3 tests) 36 (18.0%), severe CAN (≥4 or OH) 8 (4.0%). CAN prevalence correlated significantly with diabetes duration (r=0.41) and HbA1c (r=0.34). Independent predictors of definite/severe CAN: diabetes duration >10 years (aOR 3.2), HbA1c ≥8% (aOR 2.1), retinopathy (aOR 2.4), and microalbuminuria (aOR 1.9). **Conclusion:** CAN affects 44% of long-standing T2DM patients and is independently predicted by poor glycaemic control, diabetes duration, retinopathy, and nephropathy. Ewing's battery should be incorporated into annual diabetic complication screening, with particular attention to patients with HbA1c ≥8% and duration >10 years.

Keywords: Cardiac autonomic neuropathy; Ewing's battery; type 2 diabetes; heart rate variability; glycaemic control; diabetic neuropathy; sudden cardiac death

1. INTRODUCTION

A major clinically significant yet underdiagnosed microvascular complication of diabetes mellitus is cardiac autonomic neuropathy (CAN). Diabetics with CAN have impaired autonomic control of the cardiovascular system after excluding other causes, with symptoms ranging from subclinical sympatho-vagal imbalance detected only by heart rate variability to overt autonomic failure manifesting as resting tachycardia, fixed heart rate, and orthostatic

hypotension [1]. Several meta-analyses have demonstrated the clinical consequences: a meta-analysis by Maser et al. In [2], cardiovascular mortality is associated with CAN with a relative risk of 3.45 (95% CI 2.66–4.47), independent of conventional risk factors. This is the highest risk estimate of any T2DM complications. This condition is characterized by progressive loss of cardiac sympathetic and parasympathetic nerve fibers that supply the sinoatrial node, myocardium, and coronary arteries. In early CAN, the predominant signal is parasympathetic (vagal), manifesting as a reduced variation in heart rate, a blunted response to deep breathing, and a shortening of QTc intervals. As CAN progresses, sympathetic denervation supervenes, resulting in resting tachycardia (loss of vagal braking), impaired QTc adaptation, heightened cardiovascular stress responsiveness, and ultimately the fixed heart rate and orthostatic hypotension of severe autonomic failure [3]. The prolonged QT interval associated with advanced CAN represents a substrate for malignant ventricular arrhythmias and is hypothesised to underlie the 'dead in bed' syndrome observed in young diabetic patients [4].

The Ewing battery a standardised set of five non-invasive cardiovascular autonomic reflex tests (CARTs) developed by Ewing et al. in 1985 [5] remains the most widely validated and clinically accessible tool for CAN assessment. The five tests assess both parasympathetic (HR response to deep breathing, Valsalva ratio, 30:15 ratio) and sympathetic (BP response to standing, BP response to sustained handgrip) cardiovascular autonomic function, allowing graded classification of CAN severity. The 2017 Toronto Consensus Panel on Diabetic Neuropathy endorsed Ewing's battery as the primary clinical CAN assessment tool, recommending annual screening in all T2DM patients with diabetes duration >5 years [6].

Despite its clinical importance and validated screening tools, CAN screening remains inconsistent in Indian diabetic care, often omitted in resource-constrained outpatient settings where glycaemic monitoring and retinal screening take priority. Published Indian data on CAN prevalence are limited and heterogeneous (14–72% depending on the population studied and definition used) [7,8]. This study was designed to determine the prevalence and grade of CAN using Ewing's battery in a systematically characterised cohort of long-standing T2DM patients at a tertiary care hospital, and to identify independent clinical and glycaemic predictors.

2. MATERIALS AND METHODS

2.1 Study Design and Population

Cross-sectional study in the diabetology OPD and general medicine ward of a tertiary care hospital over 12 months. Inclusion: (1) T2DM diagnosis ≥5 years; (2) Age 30–70 years; (3) Stable diabetes management (no insulin initiation within past 3 months). Exclusion: (1) Any condition independently causing autonomic neuropathy (alcoholism, hypothyroidism, B12 deficiency, Parkinson's disease, systemic amyloidosis, chronic kidney disease Stage 4–5); (2) Medications affecting autonomic function within 48 hours (beta-blockers, calcium channel blockers, clonidine, anticholinergics); (3) Recent acute illness (MI within 6 months, unstable angina, heart failure NYHA Class III–IV); (4) Inability to perform Valsalva manoeuvre (recent eye/abdominal surgery). Sample size: expected CAN prevalence 35% at 95% CI, 7% absolute precision — minimum n=179; target n=200.

2.2 Ewing's Battery Protocol

Testing is performed between 9 a.m. and 12:00 after a two-hour fast, with the patient lying supine for 10 minutes before testing. Holter-quality monitoring of ECGs in real-time. In any given minute, the E:I ratio, (deep breathing) represents the maximum respiratory exchange ratio (R-E) during expiration / the minimum respiratory exchange ratio (R-R) during inspiration; normal ≥1.21, borderline 1.11–1.20, abnormal ≤1.10. (2) Valsalva ratio: forced

expiration against resistance for 15 seconds; VR = longest R-R after manoeuvre / shortest R-R during manoeuvre; normal ≥1.21, borderline 1.11–1.20, abnormal ≤1.10. (3) 30:15 ratio: HR response to standing; ratio of R-R at beat 30 / R-R at beat 15 after standing; normal ≥1.04, borderline 1.01–1.03, abnormal ≤1.00. (4) BP response to standing: BP change at 2 minutes of standing; fall ≥30 mmHg systolic = abnormal (orthostatic hypotension). (5) BP response to handgrip: sustained handgrip at 30% maximum voluntary contraction for 5 minutes; diastolic BP rise normal ≥16 mmHg; abnormal ≤10 mmHg. CAN graded: Early (1 parasympathetic test abnormal); Definite (2–3 tests abnormal); Severe (≥4 abnormal or ≥2 with OH).

2.3 Complication Assessment

HbA1c (HPLC), fasting lipid profile, eGFR (CKD-EPI), spot urinary ACR. Diabetic retinopathy: non-mydriatic fundoscopy. Peripheral neuropathy: DN4 score ≥4/10 = neuropathic pain; 10-g monofilament; VPT by biothesiometry. 24-hour Holter ECG in subset (n=40): SDNN, rMSSD, pNN50, LF/HF ratio. QTc by Bazett formula on standard 12-lead ECG.

2.4 Statistical Analysis

SPSS version 26. Statistics that describe. Comparative analysis of categorical data using the Chi-square and Fisher's exact formulas. Pearson/Spearman correlation for continuous variables. One-way ANOVA/Kruskal-Wallis for CAN grade comparisons. Multivariable binary logistic regression (outcome: definite/severe CAN ≥2 abnormal tests); aOR (95% CI); $p<0.05$ significant.

3. RESULTS

3.1 CAN Prevalence and Grade Distribution

200 T2DM patients evaluated (56.5% male; mean age 55.2 ± 9.6 years; mean diabetes duration 9.8 ± 4.6 years; mean HbA1c 8.6 ± 1.8%). CAN (≥2 abnormal Ewing's tests) was detected in 88 patients (44.0%; 95% CI 37.1–51.1%). Grade distribution: early CAN (1 abnormal test) — 44 (22.0%); definite CAN (2–3 abnormal) — 36 (18.0%); severe CAN (≥4 abnormal or OH) — 8 (4.0%). The complete clinical profile is presented in Table 1.

Table 1. Clinical and Metabolic Profile by CAN Status (n=200)

Characteristic	No CAN (n=112)	Any CAN (n=88)	p-value
(Mean + SD) Age in years	53.4 ± 9.2	57.6 ± 9.8	0.002
Male sex, n (%)	62 (55.4%)	51 (58.0%)	0.71
Diabetes duration, years (mean ±SD)	8.2 ± 4.0	11.8 ± 4.8	<0.001
(Mean + SD) HbA1c	8.1 ± 1.6	9.2 ± 1.9	<0.001
(mean + SD) BMI, kg/m2	27.2 ± 4.2	28.4 ± 4.6	0.05
Hypertension, n (%)	68 (60.7%)	62 (70.5%)	0.15
Diabetic retinopathy, n (%)	24 (21.4%)	36 (40.9%)	0.003
Peripheral neuropathy (DPN), n (%)	36 (32.1%)	52 (59.1%)	<0.001
Microalbuminuria, n (%)	26 (23.2%)	38 (43.2%)	0.003
eGFR <60, n (%)	10 (8.9%)	14 (15.9%)	0.13
Resting tachycardia >100 bpm, n (%)	4 (3.6%)	22 (25.0%)	<0.001
Men >450 ms/women >470 ms, n (%)	12 (10.7%)	28 (31.8%)	<0.001

3.2 Ewing's Test Results and Correlations

The most frequently abnormal individual Ewing's test was the E:I ratio (deep breathing; abnormal in 41.5% of all patients), followed by the 30:15 ratio (33.0%), Valsalva ratio (28.0%), BP response to standing/OH (16.0%), and BP response to handgrip (22.0%). Mean E:I ratio decreased significantly with increasing HbA1c: HbA1c <8% — 1.28±0.14; 8–9.9% — 1.18±0.11; ≥10% — 1.08±0.10 ($p<0.001$). CAN prevalence correlated positively with diabetes duration (Spearman $r=0.41$, $p<0.001$), HbA1c ($r=0.34$, $p<0.001$), and presence of retinopathy ($r=0.28$, $p<0.001$). Table 2 presents Ewing's test results by CAN grade.

***T*able 2. Ewing's Battery Results Across CAN Grade Categories (n=200)**

Ewing's Test	No CAN (n=112)	Early CAN (n=44)	Definite CAN (n=36)	Severe CAN (n=8)	p-value
E:I ratio (mean ±SD)	1.28±0.14	1.14±0.10	1.06±0.08	1.02±0.06	<0.001
Valsalva ratio (mean ±SD)	1.34±0.18	1.22±0.12	1.09±0.09	1.04±0.07	<0.001
30:15 ratio (mean ±SD)	1.12±0.08	1.04±0.06	0.99±0.05	0.96±0.04	<0.001
Orthostatic hypotension (BP fall ≥30)	0 (0.0%)	0 (0.0%)	8 (22.2%)	4 (50.0%)	<0.001
DB handgrip rise <10 mmHg	8 (7.1%)	12 (27.3%)	18 (50.0%)	8 (100%)	<0.001
QTc >450/470 ms	12 (10.7%)	14 (31.8%)	18 (50.0%)	6 (75.0%)	<0.001
Resting HR >100 bpm	4 (3.6%)	6 (13.6%)	10 (27.8%)	6 (75.0%)	<0.001

3.3 Predictors of Definite/Severe CAN

Multivariable logistic regression (Table 3) identified four independent predictors of definite or severe CAN (≥2 abnormal Ewing's tests): diabetes duration >10 years (aOR 3.2; 95% CI 1.7–6.0; $p<0.001$), diabetic retinopathy (aOR 2.4; 95% CI 1.2–4.6; $p=0.009$), HbA1c ≥8% (aOR 2.1; 95% CI 1.1–3.9; $p=0.019$), and microalbuminuria (aOR 1.9; 95% CI 1.0–3.6; $p=0.048$). Peripheral neuropathy did not independently predict CAN after adjustment, suggesting shared but partially non-overlapping risk factor profiles for sensory and autonomic neuropathy.

Table 3. Multivariable Logistic Regression: Predictors of Definite/Severe CAN (≥2 Abnormal Ewing's Tests) (n=200)

Variable	Unadj. OR (95% CI)	p-value	Adj. OR (95% CI)	p-value
Diabetes duration >10 years	4.0 (2.2–7.2)	<0.001	3.2 (1.7–6.0)	<0.001
Diabetic retinopathy	2.9 (1.6–5.4)	0.001	2.4 (1.2–4.6)	0.009
HbA1c ≥8%	2.6 (1.4–4.8)	0.002	2.1 (1.1–3.9)	0.019
Microalbuminuria	2.5 (1.4–4.5)	0.002	1.9 (1.0–3.6)	0.048
Peripheral neuropathy	2.4 (1.3–4.3)	0.004	1.5 (0.8–2.9)	0.23
Age ≥60 years	2.1 (1.2–3.8)	0.011	1.4 (0.7–2.6)	0.33
Hypertension	1.6 (0.9–2.9)	0.12	1.2 (0.6–2.2)	0.57

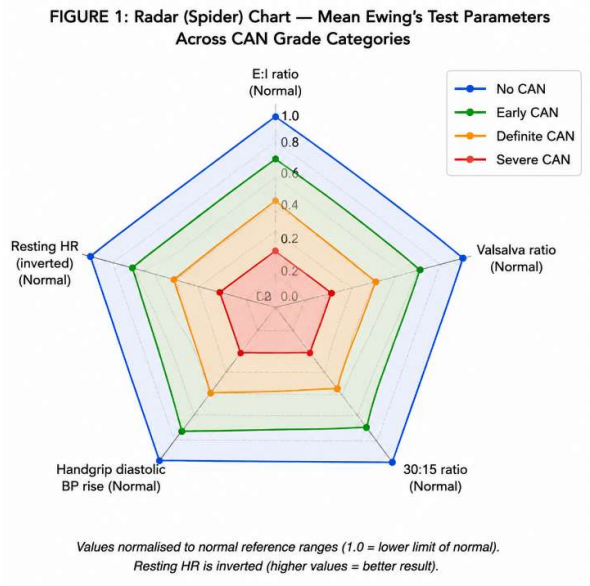

Figure 1. Radar chart illustrating mean Ewing's battery parameters (E:I ratio, Valsalva ratio, 30:15 ratio, handgrip diastolic BP rise, and resting HR) across CAN grade categories in long-standing T2DM (n=200). Progressive autonomic dysfunction is visually represented by inward contraction of each polygon from No CAN (outer, blue) to Severe CAN (inner, red).

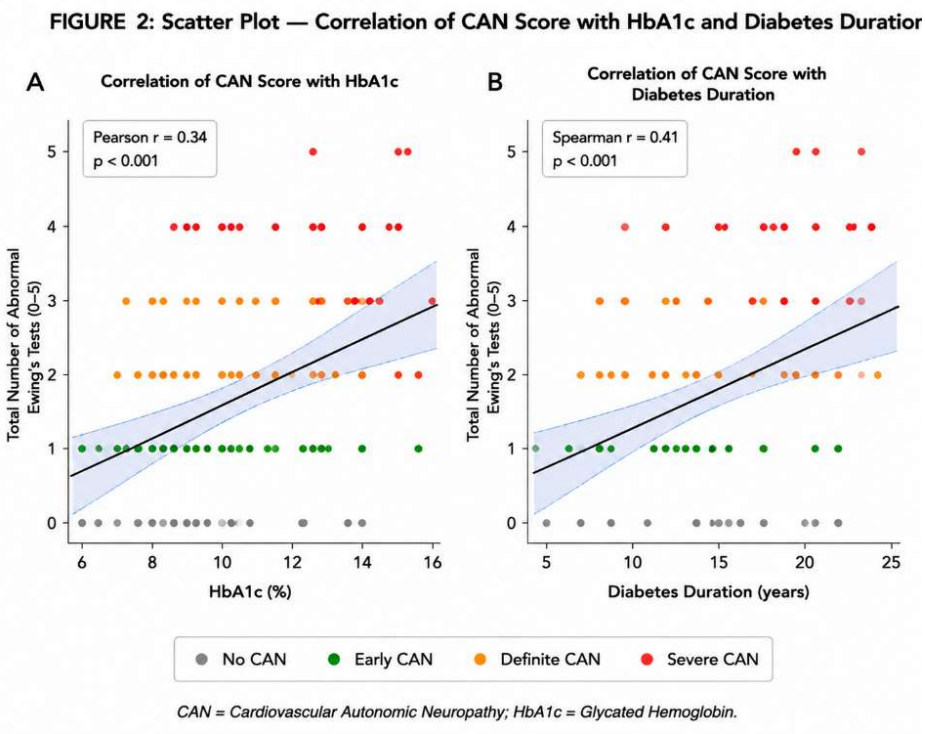

Figure 2. The correlation between (A) HbA1c % and (B) diabetes duration in years is shown in the scatter plots below in long-term T2DM patients (n=200). Both glycaemic control and

disease duration are independently associated with increasing autonomic dysfunction severity.

4. DISCUSSION

This cross-sectional study using Ewing's standardised battery detected CAN in 44.0% of long-standing T2DM patients (definite/severe CAN in 22.0%), consistent with global data. There is a 36% prevalence of CAN reported by the EURODIAB IDDM Complications Study (9) in people with type 1 diabetes, but Indian studies in people with type 2 diabetes report rates of 30–65%, depending on the definition used. The wide range in published prevalence reflects definitional heterogeneity (some studies use a single abnormal test) and population differences; our use of the ≥2 abnormal tests definition — endorsed by the Toronto Consensus Panel [9] provides a standardised, reproducible estimate.

Diabetes duration >10 years emerged as the strongest independent predictor of definite/severe CAN (aOR 3.2), consistent with the progressive, duration-dependent nature of autonomic nerve fibre degeneration [10]. As CAN severity is significantly correlated with diabetes duration (r=0.41) and HbA1c (r=0.34), it is clear that both diabetes duration and glycaemic control play independent roles in developing CAN. This is consistent with the DCCT/EDIC study, which found intensive glycaemic control reduced CAN incidence by 53% in T1DMs [11].

The independent association of diabetic retinopathy with definite/severe CAN (aOR 2.4) — after adjustment for HbA1c and diabetes duration — suggests shared microvascular injury pathways beyond glycaemic control alone. A number of overlapping molecular mechanisms contribute to both retinal capillary basement membrane thickening and autonomic nerve fiber degeneration [12]. Clinically, the presence of retinopathy should trigger CAN screening even in patients with relatively moderate HbA1c, as retinopathy may reflect a systemic microvascular susceptibility not fully captured by glycaemia alone.

Microalbuminuria as an independent CAN predictor (aOR 1.9) is consistent with the concept of a 'diabetic microvascular triopathy' — simultaneous involvement of renal, retinal, and autonomic microvasculature — where the presence of any one complication raises the likelihood of co-existing others [13]. This clustering of microvascular complications argues for a comprehensive complication screening approach rather than evaluation of individual complications in isolation.

The clinical implications of CAN are underappreciated in routine T2DM management. Resting tachycardia (present in 25.0% of CAN-positive patients) reduces cardiac diastolic filling time and increases oxygen demand, contributing to diabetic cardiomyopathy independent of ischaemic heart disease [14]. Prolonged QTc (present in 31.8% of definite CAN and 75.0% of severe CAN) represents an arrhythmogenic substrate that may explain the 'dead in bed' phenomenon and justifies periodic ECG surveillance in CAN-positive patients, with avoidance of QTc-prolonging drugs where possible [15]. Orthostatic hypotension (22.2% of definite CAN) causes debilitating falls, syncope, and indirectly reduces medication adherence — a particularly significant problem in older patients with CAN-associated impaired cerebral autoregulation [16].

Limitations: cross-sectional design precludes temporal assessment of CAN progression; absence of heart-rate spectral analysis (power spectral density) for all patients limits direct quantification of LF/HF ratio; equipment-dependent standardisation of Ewing's tests requires careful quality control; patients were recruited from a tertiary care hospital, likely representing more complex cases than community-level T2DM.

5. CONCLUSION

CAN affects 44% of long-standing T2DM patients and is independently predicted by diabetes duration >10 years, retinopathy, poor glycaemic control (HbA1c ≥8%), and microalbuminuria. Clinically significant manifestations — resting tachycardia, prolonged QTc, and orthostatic hypotension — are common in definite and severe CAN. Annual Ewing's battery screening should be incorporated into the T2DM complication assessment protocol, with particular prioritisation of patients with diabetes duration >10 years, poor glycaemic control, and co-existing retinopathy or nephropathy.

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