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Research Article

Heart Rate Variability and Ewing's Battery-Derived Cardiac Autonomic Neuropathy in Prediabetic versus Healthy Adults: A Case-Control Study from Central India

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ABSTRACT

Aims: Prediabetes affects an estimated 136 million Indian adults, with central India identified as a region of disproportionate burden. We assessed and compared heart rate variability (HRV) and Ewing's-battery-derived cardiac autonomic neuropathy (CAN) between prediabetic and healthy adults, and correlated autonomic indices with clinical and biochemical parameters.

Methods: In this age- and sex-matched case-control study, 100 prediabetic adults (ADA 2024 criteria) and 100 healthy controls underwent anthropometric and biochemical assessment, 5-minute resting HRV recording, and the five-test Ewing battery. Between-group comparisons used the independent t-test/Mann-Whitney U test, Chi-square/Fisher's exact test, Pearson/Spearman correlation, and multiple linear regression (α=0.05).

Results: All time- and frequency-domain HRV parameters and all five Ewing-battery components were significantly impaired in prediabetic participants ($p<0.001$). CAN, graded by composite Ewing score, was present in 100% of prediabetic participants (63% Early, 21% Definite, 16% Severe) versus 3% of controls ($p<0.001$). Within the prediabetic group, waist circumference, not BMI or glycaemic indices, was the only significant independent predictor of SDNN (β=−0.68 ms/cm, $p=0.019$; model $R^2=0.114$).

Conclusions: Cardiac autonomic dysfunction is already measurable, and in this cohort near-universal, in prediabetic adults, and correlates more consistently with central adiposity than with glycaemia. These findings support incorporating brief, non-invasive autonomic screening into the routine evaluation of prediabetic individuals in high-burden Indian populations.

Keywords: Prediabetes, Heart Rate Variability, Cardiac Autonomic Neuropathy, Ewing's Battery, Waist Circumference, India.

INTRODUCTION

Prediabetes affects an estimated 636 million adults worldwide and 136 million adults in India, with the ICMR-INDIAB national survey specifically identifying Madhya Pradesh and Rajasthan as states in which the prediabetic pool is disproportionately large relative to overt diabetes[1,2]. Cardiac autonomic neuropathy (CAN), a complication of dysglycaemia mediated by oxidative stress, polyol-pathway flux, and advanced-glycation-end-product accumulation in autonomic nerve fibres, carries independent prognostic significance for cardiovascular mortality that is well established in post-infarction and general populations[3,4,5]. Increasing evidence indicates that autonomic dysfunction is measurable well before the diagnostic threshold for diabetes is crossed[6,7], most authoritatively in the Maastricht Study, a large population-based cohort in which both prediabetes and type 2 diabetes were independently associated with lower heart rate variability (HRV) after multivariable adjustment[6], a finding subsequently confirmed by systematic review[7].

Despite this international evidence, India-specific data remain limited to a single small case-control study[8], and no published study from central India, the region the national data specifically flag as being of concern[2], was identified. Furthermore, most studies employ either spectral HRV analysis or Ewing's battery of cardiovascular reflex tests in isolation, despite evidence that the two methods are physiologically complementary[9,10], and few examine the relative contribution of adiposity versus glycaemia to autonomic impairment specifically within the narrow prediabetic glycaemic band. We therefore conducted an age- and sex-matched case-control study combining spectral HRV analysis and the full Ewing battery in prediabetic and healthy adults

from a central Indian tertiary-care population, to (i) compare HRV and Ewing-battery performance between groups, (ii) determine CAN prevalence, and (iii) identify independent clinical/biochemical correlates of autonomic impairment.

SUBJECTS AND METHODS

Study Design and Population

This comparative, cross-sectional case-control study was conducted in the Department of Medical Physiology, Malwanchal University, Indore, Madhya Pradesh, over approximately 18 months. Group I comprised 100 adults newly identified with prediabetes per American Diabetes Association 2024 criteria (fasting plasma glucose 100-125 mg/dL, and/or 2-hour post-load glucose 140-199 mg/dL on a 75-g OGTT, and/or HbA1c 5.7-6.4%)[11], confirmed on two occasions. Group II comprised 100 age- (±3 years) and sex-matched, apparently healthy adults with normal glucose tolerance (fasting plasma glucose <100 mg/dL, HbA1c <5.7%). Exclusion criteria were established diabetes, cardiac arrhythmia or structural heart disease, medications affecting autonomic function, non-diabetic peripheral/autonomic neuropathy, and current smoking or regular alcohol use. Sample size (n=96/group minimum) was calculated using Cochran's formula (Z=1.96, p=0.50, d=0.10, +10% non-response), based on published precedent[8]. The study was approved by the Institutional Ethics Committee and conducted per the Declaration of Helsinki[12] and ICMR National Ethical Guidelines[13]; written informed consent was obtained from all participants.

Anthropometric and Biochemical Assessment

Height, weight (BMI = weight/height²), and waist circumference (midpoint between lowest rib and iliac crest) were measured using standard techniques. Resting blood pressure was recorded seated, after 5 minutes' rest. Following an overnight fast, fasting plasma glucose (FPG), 2-hour post-load glucose (75-g OGTT), HbA1c (HPLC), and a fasting lipid profile were estimated in a single accredited laboratory.

Heart Rate Variability and Ewing's Battery

Short-term (5-minute), supine, resting HRV was recorded using a 12-lead digital ECG/HRV-analysis system following the 1996 Task Force standards[9], after 10 minutes' rest, overnight fast, and 12-hour caffeine/tobacco/exercise abstention. Time-domain (SDNN, RMSSD, pNN50) and frequency-domain (total power, LF, HF, LF/HF ratio) parameters were derived by Fast Fourier Transform after artefact removal. All five components of Ewing's battery (heart-rate response to deep breathing, 30:15 ratio, Valsalva ratio, postural systolic-BP fall, and diastolic-BP rise with handgrip)[10] were performed and graded (normal/borderline/abnormal) against standard cut-offs, combined into a composite score (0-5) and CAN grade (Normal/Early/Definite/Severe).

Statistical Analysis

Data were analysed in a validated statistical computing environment (Python, SciPy/statsmodels). Normality was assessed by Shapiro-Wilk test; normally distributed variables were compared by independent t-test (mean±SD) and non-normally distributed variables by Mann-Whitney U test (median [IQR]). Categorical variables were compared by Chi-square/Fisher's exact test. Correlations used Pearson's or Spearman's coefficient as appropriate; multiple linear regression identified independent predictors of SDNN after adjustment for age, sex, BMI, waist circumference, systolic BP, and HbA1c. Two-tailed $p<0.05$ was considered significant.

RESULTS

Group I and Group II were well matched for age (median 46.0 vs 46.5 years, p=0.485), sex distribution (67M/33F vs 56M/44F, p=0.146), and BMI (p=0.759), but Group I showed significantly higher systolic and diastolic BP, and, as expected from the diagnostic criteria used, significantly higher FPG, 2-hour PG, and HbA1c (all $p<0.001$; Table 1).

Table 1. Baseline demographic, anthropometric, and biochemical characteristics

Variable	Group I (n=100)	Group II (n=100)	p-value
Age (years)[a]	46.0 (40.0–52.3)	46.5 (38.0–55.0)	0.485
BMI (kg/m²)[a]	25.2 (21.5–28.9)	25.4 (22.0–29.2)	0.759
Waist circumference (cm)[b]	87.2 ± 8.1	87.0 ± 8.7	0.907
Systolic BP (mmHg)[a]	134.0 (125.8–140.3)	126.0 (117.8–131.0)	<0.001
FPG (mg/dL)[a]	111.5 (106.0–118.0)	91.0 (86.0–95.0)	<0.001
HbA1c (%)[a]	6.00 (5.90–6.20)	5.20 (5.10–5.40)	<0.001

[a]Median (IQR), Mann-Whitney U test. [b]Mean±SD, independent t-test.

All time-domain and frequency-domain HRV parameters were significantly reduced in Group I, with a significantly higher LF/HF ratio, consistent with combined parasympathetic withdrawal and relative sympathetic predominance (Table 2). All five Ewing-battery components were significantly worse in Group I, with a markedly higher composite Ewing score (median 3.0 [2.5–3.0] vs 0.0 [0.0–0.5], p<0.001).

Table 2. Heart rate variability and Ewing's battery parameters by group

Parameter	Group I (n=100)	Group II (n=100)	p-value
SDNN (ms)	33.0 (28.0–39.0)	57.5 (49.8–64.0)	<0.001
RMSSD (ms)	23.0 (19.0–26.0)	37.0 (29.0–44.0)	<0.001
HF power (ms²)	324.0 (212.3–436.5)	916.5 (675.0–1169.5)	<0.001
LF/HF ratio	1.88 (1.24–2.49)	0.89 (0.72–1.22)	<0.001
E:I ratio	1.12 (1.08–1.15)	1.31 (1.24–1.36)	<0.001
Valsalva ratio	1.13 (1.11–1.16)	1.36 (1.29–1.43)	<0.001
Composite Ewing score (0–5)	3.0 (2.5–3.0)	0.0 (0.0–0.5)	<0.001

All values are median (IQR); Mann-Whitney U test (Shapiro-Wilk p<0.05 for all variables).

CAN, graded by composite Ewing score, was present in 100% of Group I (63% Early, 21% Definite, 16% Severe) versus 3% of Group II (all Early; $\chi2=188.5$, df=3, p<0.001; Table 3, Fig. 1). Within Group I, correlations between autonomic parameters and clinical/biochemical variables were largely weak; the strongest were BMI with LF/HF ratio (r=0.26, p=0.009) and BMI with HF power (r=−0.21, p=0.038). No glycaemic index correlated significantly with any HRV or Ewing parameter. On multiple regression, waist circumference was the only significant independent predictor of SDNN (β=−0.68 ms/cm, 95% CI −1.25 to −0.12, p=0.019); BMI, HbA1c, age, sex, and systolic BP were not significant (model $R^2=0.114$, F=2.00, p=0.073).

Table 3. CAN grade distribution by group

CAN Grade	Group I, n (%)	Group II, n (%)
Normal	0 (0)	97 (97)
Early	63 (63)	3 (3)
Definite	21 (21)	0 (0)
Severe	16 (16)	0 (0)

$\chi2=188.5$, df=3, p<0.001.

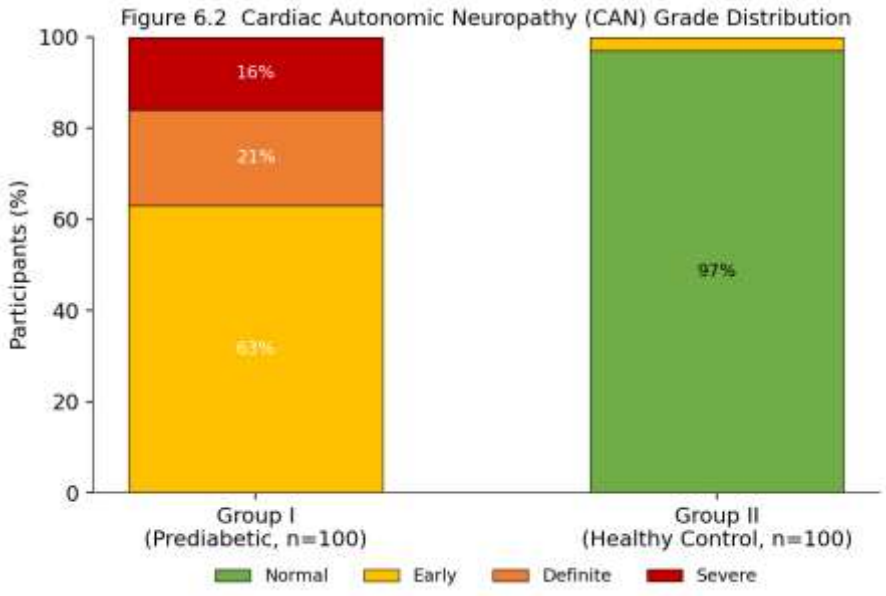

Fig. 1. Cardiac autonomic neuropathy (CAN) grade distribution by group.

DISCUSSION

Every HRV and Ewing-battery parameter was significantly impaired in prediabetic adults relative to matched controls, and CAN was present in the great majority of prediabetic participants, in a pattern and direction consistent with the Maastricht Study[6] and the Eleftheriadou systematic review[7], and closely mirroring the only comparable Indian precedent[8]. The magnitude of separation observed here, however, exceeds that typically reported in larger, multi-centre cohorts[6,7], and should be interpreted with appropriate caution pending independent, multi-centre replication; plausible contributors include the single-centre, single-observer design, which removes inter-site variability, and the narrow 30-60-year age band with strict exclusion criteria, both of which would be expected to sharpen rather than blur the case-control distinction.

The pattern of more uniformly affected heart-rate-based tests relative to blood-pressure-based tests is consistent with the length-dependent model of autonomic injury first described by Ewing[10], under which the vagus, as the longest autonomic nerve, is affected earliest[3,14]. Within Group I, waist circumference, rather than BMI or any glycaemic index, was the only significant independent predictor of SDNN, corroborating an earlier report that waist-hip ratio, but not BMI, correlates with reduced HRV[15], and consistent with the Landsberg hypothesis, under which hyperinsulinaemia associated with central obesity chronically stimulates sympathetic activity independently of the degree of hyperglycaemia[16]. The absence of a significant glycaemia-HRV correlation within our narrow prediabetic band, in apparent contrast to the full-spectrum Maastricht analysis[6], is most plausibly a range-restriction artefact rather than a genuine discrepancy.

The clinical significance of these findings rests on the well-established prognostic weight of autonomic markers in other populations: in the ATRAMI study, reduced HRV and baroreflex sensitivity independently predicted post-infarction cardiac mortality[4], and reduced HRV independently predicted incident cardiac events even in an asymptomatic Framingham cohort[5]. Given the disproportionately large prediabetic pool identified in this region by national survey data[2], our findings support incorporating brief, non-invasive autonomic screening, at minimum the heart-rate response to deep breathing, into the routine evaluation of newly identified prediabetic individuals.

Limitations include the cross-sectional design, which precludes causal inference; short-term rather than 24-hour HRV recording, in keeping with feasibility for outpatient screening; single-centre sampling; and the absence of fasting insulin/HOMA-IR measurement, which would have permitted more direct mechanistic testing of the adiposity-autonomic relationship observed.

CONCLUSIONS

Cardiac autonomic dysfunction, assessed by both spectral HRV analysis and Ewing's battery, is already measurable, and in this cohort near-universal, in prediabetic adults from central India, and correlates more consistently with central adiposity than with glycaemic status. These findings support incorporating brief, non-invasive autonomic screening, and closer anthropometric surveillance, into the routine evaluation of prediabetic individuals in high-burden Indian populations, and warrant confirmation in larger, multi-centre cohorts.

Declarations

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest: The authors declare no conflict of interest.

Ethical approval: The study was approved by the Institutional Ethics Committee, Malwanchal University, Indore, and conducted in accordance with the Declaration of Helsinki.

Informed consent: Written informed consent was obtained from all participants.

Data availability: The datasets generated during the current study are available from the corresponding author on reasonable request.

Author contributions (CRediT): Anil Kumar: Investigation, Data curation, Formal analysis, Writing – original draft. Manila Jain: Conceptualization, Methodology, Supervision, Writing – review & editing.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas. 11th ed. Brussels: International Diabetes Federation; 2025.
2. Anjana RM, Unnikrishnan R, Deepa M, Pradeepa R, Joshi SR, Bhansali A, et al. Metabolic non-communicable disease health report of India: the ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). Lancet Diabetes Endocrinol. 2023;11(7):474-89.

3. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care. 2003;26(5):1553-79.
4. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ; ATRAMI Investigators. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. Lancet. 1998;351(9101):478-84.
5. Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, et al. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation. 1996;94(11):2850-5.
6. Coopmans C, Zhou TL, Henry RMA, Heijman J, Schaper NC, Koster A, et al. Both prediabetes and type 2 diabetes are associated with lower heart rate variability: the Maastricht study. Diabetes Care. 2020;43(5):1126-33.
7. Eleftheriadou A, Williams S, Nevitt S, Brown E, Roylance R, Wilding JPH, et al. The prevalence of cardiac autonomic neuropathy in prediabetes: a systematic review. Diabetologia. 2021;64(2):288-303.
8. Gujjar P, Ravikumar YS, Nagendra L, Boro H, Bhattacharya S. Cardiac autonomic neuropathy in prediabetes: a case-control study. Indian J Endocrinol Metab. 2023;27(4):325-9.
9. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Circulation. 1996;93(5):1043-65.
10. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years' experience in diabetes. Diabetes Care. 1985;8(5):491-8.
11. American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: Standards of Care in Diabetes-2024. Diabetes Care. 2024;47(Suppl 1):S20-42.
12. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-4.
13. Indian Council of Medical Research. National Ethical Guidelines for Biomedical and Health Research Involving Human Participants. New Delhi: ICMR; 2017.
14. Edwards JL, Vincent AM, Cheng HT, Feldman EL. Diabetic neuropathy: mechanisms to management. Pharmacol Ther. 2008;120(1):1-34.
15. Yadav RL, Yadav PK, Yadav LK, Agrawal K, Sah SK, Islam MN. Association between obesity and heart rate variability indices: an intuition toward cardiac autonomic alteration - a risk of CVD. Diabetes Metab Syndr Obes. 2017;10:57-64.
16. Landsberg L. Diet, obesity and hypertension: an hypothesis involving insulin, the sympathetic nervous system, and adaptive thermogenesis. Q J Med. 1986;61(236):1081-90.