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Cardiac Autonomic Neuropathy in Type 2 Diabetes: Prevalence and Risk Factors

Kashif Bin Naeem*, Vinod Choondal, Suad Hannawi, Abdalla Alhajiri and Sreevidya Machinga

Al Kuwait Hospital, Ministry of Health and Prevention, Dubai, UAE.

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ABSTRACT

Cardiac autonomic neuropathy (CAN) is a common complication of diabetes mellitus that is strongly associated with an increased risk of silent myocardial ischemia and mortality.

Despite the serious implications, it is frequently overlooked and under-diagnosed. Hence, we conducted a prospective analysis of 62 consecutive type 2 diabetic patients and used ECG-based heart rate variability testing to diagnose CAN during (a) deep breathing (rate 6/min) and (b) standing to measure 30:15th beat ratio. CAN was diagnosed if the co-efficient of variation of R-R interval was found to be less than 2.

Results: Mean age 60 ± 8 years. 35/62 (56%) tested positive for CAN. Logistic regression analysis revealed that CAN patients were older (62 vs. 57 years, p=0.02), had lower eGFR (86 vs. 105 ml/min, p=0.009) and had hypertension (86% vs. 48%, p=0.001).

Conclusion: Cardiac autonomic neuropathy is common in type 2 diabetes. Associated risk factors include older age, hypertension and low eGFR

Keywords: Diabetes mellitus, Cardiac autonomic neuropathy, Heart rate variability

Abbreviations: DM: Diabetes Mellitus; CAN: Cardiac Autonomic Neuropathy; HRV: Heart Rate Variability; eGFR: estimated Glomerular Filtration Rate; CKD: Chronic Kidney Disease

INTRODUCTION

Cardiac Autonomic Neuropathy (CAN) is a serious complication of Diabetes Mellitus (DM) that is among the least recognized and understood. Not only does it affect the survival and quality of life in diabetics [1-3], it is also a major source of increased cost in the diabetic care. DM commonly leads to diffuse and widespread damage to nerves (peripheral and autonomic) and small vessels. Autonomic neuropathy once recognized a late complication of diabetes, now may arise as early as the time of diagnosis [4]. The prevalence is highly variable depending on the diagnostic criteria and the population studied. It ranges from as low as 1.6-2.6% of the primary prevention cohort in the Diabetes Control and Complications Trial (DCCT) [5] to as high as 90% of patients with longstanding type 1 diabetes who were potential candidates for a pancreas transplant [6]. CAN is a significant cause of morbidity and mortality independent of cardiovascular risk factors in various populations [7-10] including silent myocardial ischemia. Clinical manifestations of CAN include resting tachycardia, postural hypotension, exercise intolerance, enhanced intraoperative or perioperative cardiovascular lability, increased incidence of asymptomatic ischemia, myocardial infarction and decreased rate of survival after myocardial infarction [11]. Availability of non-invasive tests has now made it possible to diagnose CAN at an early stage, thus allowing earlier intervention when the condition is still reversible. The present study has been conducted with an objective to estimate the prevalence of CAN in type 2 diabetics and determine the associated risk factor.

Corresponding author: Kashif Bin Naeem, Consultant Cardiologist, Ministry of Health and Prevention, Dubai, UAE, Tel: +971 569443145; E-mail: kbncardiology@yahoo.co.uk

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METHODOLOGY

Study population

From January 2018 to March 2019, 62 patients with type 2 DM were recruited consecutively at the Diabetic Clinic, Al Kuwait Hospital, Dubai, UAE. Patients were excluded if they were younger than 18 years, had type 1 DM, had known coronary heart disease, COPD or asthma on inhalers, who were taking heart rate limiting medications or were not capable of giving informed consent.

Consent

All participants signed informed consent before beginning the study.

Ethical approval

The study has been approved by Dubai Research and Ethics Committee, UAE.

Data collection

At the beginning of the study, baseline information was collected regarding history of hypertension, smoking and dyslipidemia; anti-diabetic medications; use of aspirin and statin; autonomic symptoms, body mass index; blood pressure and resting heart rate. Laboratory tests were done to measure glycated hemoglobin, eGFR and lipid profile.

Assessment of cardiac autonomic neuropathy (CAN)

All participants underwent cardiac autonomic function testing that was performed by a trained technician. Patients were instructed to avoid caffeine and nicotine for 8 h before the test. Also, sympathomimetic and anticholinergic drugs were avoided 48 h pre-testing. Patients were asked to lie down or sit quietly for 30 min before commencing the test. The tests were done using Neuropack X1-QP-259BK software with Nihon Kohden operating system. We employed two maneuvers to assess the parasympathetic autonomic system. The tests involved measuring the heart rate variability (HRV) non-invasively as proposed by Ewing et al. [12]. Patients were tested during (a) deep breathing; and (b) postural change from lying to standing. For deep breathing, the patient was asked to lie quietly and breathe deeply at a rate of 6/min. The ECG monitor then recorded the difference between the maximum and minimum heart rate. HRV was also measured on standing from supine by analyzing the ratio of longest R-R interval (found at about beat 30) to the shortest R-R interval (found at about beat 15). CAN was diagnosed if the co-efficient of variation of R-R interval was found to be less than 2.

STATISTICAL ANALYSIS

Results are expressed as percentages for categorical variables, and mean ± SD for continuous variables. Unpaired two sample (independent) student's t-test was used for the differences between the mean values of the continuous variables. Chi^2 test was used for the categorical variables.

Logistic regression was used to analyze the correlation between the presence of CAN and the continuous variables. Statistical significance was accepted as p-value<0.05. Multivariate model was built using all the variables that were included in the univariate models. For all the analysis, Stata 9/SE (Stata Corp, College Station, Tx, USA) statistical software was used.

RESULTS

Total of 62 type 2 diabetic patients were involved in the study.

Table 1 depicts the demographic details, clinical and laboratory values of the participants. Mean age was 60 ± 8 years; 55% were females; 69% hypertensive; 55% dyslipidemic; mean BMI 31 kg/m^2. Mean BP was 131/72 mm Hg; mean HbA1c 7.6%; mean LDL 2.4 mmol/L; mean eGFR 95 ml/min. 35/62 (56%) tested positive for the presence of cardiac autonomic neuropathy.

Table 2 compares the characteristics in the two groups (with and without CAN). Those with CAN were older in age than patients without CAN (62 vs. 57 years, p=0.02); had lower eGFR (86 vs. 105 ml/min, p=0.009) and were more hypertensive (86% vs. 48%, p=0.001).

Table 3 represents univariate logistic regression analysis that revealed significant positive association between the presence of CAN and the age of the participants (OR 1.08, P=0.02). There was a negative association found between the presence of CAN and the eGFR level (OR 0.97, P=0.01). Multivariate logistic regression analysis included all the variables that were used in the univariate analysis and showed that the only variable that maintained a significant association with the presence of CAN was the eGFR level (OR 0.97, P-0.04).

Table 1. Baseline characteristics.

Demographics	**n=62**
Age (years), mean (SD)	60 (8)
Gender (F:M), n (%)	34 (55%):28 (45%)
Hypertension, n (%)	43 (69)
Dyslipidemia, n (%)	34 (55)
Smoking, n (%)	8 (13)
BMI (kg/m^2), mean (SD)	31 (6)
SBP (mmHg), mean (SD)	131 (15)
DBP (mm Hg), mean (SD)	72 (10)
Resting heart rate/min, mean (SD)	81 (10)
Medications	
Oral anti diabetics, n (%)	37 (60)
Oral+insulin, n (%)	23 (37)
Aspirin, n (%)	25 (40)
Statin, n (%)	51 (82)
Symptoms	
Sensory, n (%)	31 (50)
Motor, n (%)	3 (5)
Autonomic, n (%)	9 (15)
Laboratory values	
HbA1c (mmol/L), mean (SD)	7.6 (2)
eGFR (ml/min), mean (SD)	95 (30)
Total cholesterol (mmol/L), mean (SD)	4 (1)
Triglyceride (mmol/L), mean (SD)	1 (0.6)
HDL (mmol/L), mean (SD)	1 (0.3)
LDL (mmol/L), mean (SD)	2.4 (0.9)

Data presented as mean (SD) or n (%)
BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HbA1c: Glycosylated Hemoglobin; eGFR: estimated Glomerular Filtration Rate; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein

Table 2. Comparison of the diabetic patients with and without cardiac autonomic neuropathy (CAN).

Variables	DM without CAN	DM with CAN	P value
Age (years), mean (SD)	57 (8)	62 (7)	0.021
Gender (M:F), n	10:17	18:17	0.259
Hypertension, n (%)	13 (48%)	30 (86%)	0.001
Dyslipidemia, n (%)	16 (59%)	18 (51%)	0.539
Smoking, n (%)	24 (89%)	30 (86%)	0.712
Oral diabetic medications, n (%)	19 (60%)	18 (51%)	0.132
Oral diabetic medications + insulin, n (%)	7 (13%)	16 (46%)	0.110
Use of Aspirin, n (%)	11 (41%)	14 (40%)	0.953
Use of Statin, n (%)	25 (93%)	26 (74%)	0.061
Sensory symptoms, n (%)	12 (44%)	19 (54%)	0.442
Motor symptoms, n (%)	1 (4%)	2 (6%)	0.715
Autonomic symptoms, n (%)	2 (7%)	7 (20%)	0.163
BMI (kg/m^2), mean (SD)	30 (5)	31 (7)	0.576
SBP (mm Hg), mean (SD)	129 (14)	132 (15)	0.3996
DBP (mm Hg), mean (SD)	72 (9)	71 (11)	0.621
Resting heart rate/min, mean (SD)	79 (8)	81 (10)	0.399
HbA1C (mmol/L), mean (SD)	7 (1)	8 (2)	0.366
GFR (ml/min), mean (SD)	105 (26)	86 (30)	0.009
Total Cholesterol (mmol/L), mean (SD)	4.154 (0.957)	4.008 (1.090)	0.583
Triglyceride (mmol/L), mean (SD)	1.487 (0.841)	1.395 (0.531)	0.601
HDL (mmol/L), mean (SD)	1.242 (0.337)	1.196 (0.346)	0.602
LDL (mmol/L), mean (SD)	2.462 (0.885)	2.317 (0.951)	0.540

Data presented as mean (SD) or n(%). Significant p value of <0.05

Table 3. Logistic regression analysis of the relationship between CAN in Diabetic patients with each of the demographic variables, clinical and laboratory values.

Variables	OR	SE	Z	P value	CI
Univariate logistic regression					
Age	1.082	0.039	2.21	0.027	1.009, 1.162
BMI (kg/m^2)	1.024	0.044	0.57	0.571	0.941, 1.116
SBP (mm Hg)	1.015	0.018	0.85	0.394	0.980, 1.052
DBP (mm Hg)	0.987	0.024	-0.50	0.614	0.940, 1.037
Resting heart rate/min	1.023	0.027	0.85	0.393	0.970, 1.079
HbA1C (%)	1.161	0.192	0.90	0.368	0.839, 1.606
GFR (ml/min)	0.976	0.009	-2.44	0.015	0.957, 0.995
Total cholesterol (mmol/l)	0.869	0.218	-0.56	0.578	0.531, 1.423
TG (mmol/l)	0.816	0.312	-0.53	0.596	0.385, 1.729
HDL (mmol/l)	0.669	0.507	-0.53	0.597	0.151, 2.955
LDL (mmol/l)	0.839	0.237	-0.62	0.535	0.481, 1.461
Multivariate logistic regression					
GFR (mm Hg)	0.976	0.011	-2.05	0.040	0.955, 0.998

All the parameters in the univariate logistic regression have been included in the multivariate logistic regression analysis
Only the significant parameter in the multiple logistic regressions is displayed. Significant p value of <0.05
OR: Odd Ratio; SE: Standard Error; CI: Confidence Interval

DISCUSSION

Our study has shown the prevalence of CAN to be 56% in type 2 diabetics. This corresponds to the findings of an epidemiological study that suggested that almost 50-77% of the diabetic patients had evidence of CAN [13].

CAN have several risk factors that are common to other diabetes-related vascular complications, such as glycemic control, diabetes duration, and cardiovascular disease risk factors, among others. In the EURODIAB prospective complications study, risk factors related to CAN development were investigated over a 7.3 year follow-up in patients with T1DM. The study showed that systolic blood pressure (SBP; OR 1.1/10 mm Hg, 95% CI 1-1.3), HbA1c (OR 1.2 per percentage point, 95% CI 1.1-1.4) and age (OR 1.3 per decade, 95% CI 1.1-1.7) were associated with a higher risk of developing CAN [14]. A cross-sectional study of 2,230 participants with T2DM also showed that CAN patients had a higher prevalence of hypertension vs. patients without CAN (57% vs. 49%, P<0.001) [15]. Our study showed that the risk of developing CAN was profound with increasing age and hypertension.

CAN is also strongly associated with chronic kidney disease (CKD) in diabetics. A study performed on 20 diabetic patients with CKD found that all CKD patients had evidence of CAN as tested by the heart rate response to standing [16]. Out study found significant correlation of CAN with lower eGFR values.

The tests to diagnose CAN were first described by Ewing et al in 1980 [17]. These included heart rate response to deep breathing, standing, valsalva maneuver, BP response to standing and sustained muscle contraction. The CAN subcommittee of the Toronto Consensus Panel defined definite CAN as the presence of at least two abnormal tests, presence of one abnormal test as possible CAN and presence of orthostatic hypotension with two or more abnormal tests as indicative of advanced CAN [18]. These tests are the gold standard in clinical autonomic testing, as they are all noninvasive, safe and well standardized. Pafili et al. [19] compared the results from each individual test and their combination against Ewing's battery of tests. The study included 152 patients with median diabetes duration of 12 years and mean age of 64.51 ± 7.85 years. It was concluded that the heart rate response to standing with 30:15 ratio demonstrated the best diagnostic indicator for CAN, with 96% sensitivity, 65% specificity, 94% negative predictive value and OR of 21.14. It also suggested that if a 30:15 ratio indicated CAN, diagnostic accuracy could be increased if combined with the valsalva ratio, a rise in DBP and/or E:I ratio (heart rate response to deep breathing). Based on the

availability of expertise and equipment, we employed two tests in our study to diagnose CAN: heart rate response to deep breathing and standing. These tests are well validated and provide reliable diagnostic accuracy.

Early diagnosis of CAN is essential to abolish symptoms or reduce progression. The disease may be reversible if diagnosed soon after onset. Current methods use a combination of non-pharmacological and pharmacological approaches, including lifestyle modification, intensive glycemic control and treating underlying risk factors, such as hyperlipidemia and hypertension. Increased physical activity has been demonstrated to improve heart rate variability and resting heart rates. A review by Voulgari et al. [20] concluded that moderate endurance and aerobic exercise improved HRV and parasympathetic dominance in patients with T1DM or T2DM. The effect of intensive glycemic control on CAN is well described for type 1 DM but unclear in type 2 DM. The Veterans Affairs Cooperative Study suggested no impact of intensive glycemic control on CAN [21]. Conversely, the STENO-2 trial demonstrated that intensive multifactorial treatment (including behavior modification and intensive therapy targeting hyperglycemia and CVD risk factors) lowered progression to CAN in type 2 DM (OR 0.32, 95% CI 0.12-0.78); these benefits were sustained at the 2-year follow-up [22].

Our study has its limitations. The sample size was less; not all non-invasive tests were employed; and no follow up was reported to assess the prognosis.

CONCLUSION

Cardiac autonomic neuropathy is common in type 2 diabetics, with prevalence of more than 50% in our study. Heart rate variability testing with maneuvers like standing and deep breathing is useful to diagnose CAN. Older people, hypertensive and those with low eGFR are risk factors to develop CAN.

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