



# Prevalence and Associated Factors of Cardiac Autonomic Neuropathy Among Diabetic Patients at Bugando Medical Centre, Mwanza, Tanzania

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## Abstract

**Introduction:** DM has been implicated with multiple complications including diabetic cardiac autonomic neuropathy (DCAN), with a global burden ranging from 1% - 90% in type 1 DM and 20% - 73% in type 2 DM. Poor glycemic control, long duration of DM and traditional cardiovascular risk factors have been associated with the development and progression of DCAN. In Tanzania, there is limited data on DCAN burden and its associated factors. This study was conducted to raise awareness about DCAN, so as to establish protocols and guidelines for better diabetes management and control. **Methodology:** A hospital-based cross-sectional study was conducted in the DM MOPD at BMC, with a sample size of 383 DM patients. A standard questionnaire was used for Data collection, and DCAN diagnosis was made using cardiovascular autonomic reflex tests (CARTS). Data was analyzed using STATA version 15, DCAN associated factors were analyzed using bivariate logistic regression models. **Results:** Of 383 patients, 49.1% (188) had DCAN with heart rate variability being the most common abnormality 38.9% (149) and Postural hypotension being the least 2.4% (9). Obesity, presence of pathological Q and resting tachycardia were significantly associated with DCAN. Though statistically significant, Age, peripheral neuropathy, HbA1C, dyslipidemia, hypertension and DM duration were not analyzed in the final model because of multi-collinearity. **Conclusion:** DCAN is prevalent among DM patients attending MOPD at BMC. Obesity, resting tachycardia and pathological Q wave are significantly associated with DCAN. Measures should be taken to address the increase in obesity in our population. ECG should be performed in DM

patients to address the grave clinical repercussion associated with pathological Q wave.

## Subject Areas

Cardiology, Clinical Medicine

## Keywords

Diabetic Cardiac Autonomic Neuropathy: Prevalence, Associated Factors, Mwanza, Tanzania

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## 1. Background

The prevalence of Diabetes Mellitus (DM) is increasing globally in both resource rich and resource limited countries including Sub Saharan Africa (SSA). Increase in DM prevalence could partly be attributed to urbanization, an increase in life expectancy and improved diagnosis rates of DM [1] [2]. According to the International Diabetes Federation (IDF) in 2020, the global DM prevalence was 463 million people with more than 19 million people in the Africa region. In 2021, IDF reported an increase in DM prevalence from 2.8% to 12% in a period of 10 years, 2011 to 2021 in Tanzania [3].

Diabetic Cardiac Autonomic Neuropathy (DCAN) is one of the autonomic neuropathies that affect the cardiovascular system, defined as the impairment of cardiovascular autonomic control in the setting of DM after exclusion of other causes [4]. Globally, the prevalence of DCAN ranges from 1% - 90% in type 1 DM (T1DM) and 20% - 73% in type 2 DM (T2DM) [5], with a predicted annual increment of 1.8% in patients with well controlled DM [6]. This wide variation could be attributed to the inconsistent diagnostic criteria used for diagnosis of DCAN throughout the studies. Unfortunately, in SSA, there are limited numbers of studies on DCAN. Migisha *et al.* in Uganda reported a DCAN prevalence of 52.2%. However, DCAN correlation with prolonged QTc Diabetic Cardiac Autonomic Neuropathy (DCAN) is one of the autonomic neuropathies that affect the cardiovascular system, defined as the impairment of cardiovascular autonomic control in the setting of diabetes mellitus (DM) after exclusion of other causes. Globally, the prevalence of DCAN ranges from 1% to 90% in type 1 DM (T1DM) and 20% to 73% in type 2 DM (T2DM), with a predicted annual increment of 1.8% in patients with well-controlled DM. This wide variation could be attributed to the inconsistent diagnostic criteria used for the diagnosis of DCAN throughout the studies. Unfortunately, in Sub-Saharan Africa (SSA), there are limited numbers of studies on DCAN. Migisha *et al.* in Uganda reported a DCAN prevalence of 52.2%. However, in his study DCAN correlation with prolonged QTc remains unclear [7]. A 2022 study by Flora Ruhangisa in Kilimanjaro region, Tanzania revealed a prevalence of DCAN to be 32%, however, this study used QTc interval

alone in predicting prevalence of DCAN [8].

Pathophysiology of DCAN has a multifactorial cause that leads to depletion of ATP, resulting in cell necrosis and activation of the gene that is involved in neuronal damage [9] [10]. Nerve fiber damage is attributed to hyperglycemia, neurovascular insufficiency, autoimmune damage and neurohormonal growth factor deficiency resulting in hypoxia and vasoconstriction to blood supply of the neuronal system [9]-[11].

## 2. Methodology

### 2.1. Study Design and Population

A hospital based cross-sectional study conducted from June 2022 to October 2022 aimed at determining the prevalence and associated factors of cardiac autonomic neuropathy among diabetic patients attending medical outpatient clinic at Bugando Medical Centre Mwanza, Tanzania. The study recruited all adult diabetic patients aged 18 years and above regardless of the type of Dm they had and whether or not they were on medication, attending DM MOPD at BMC who gave consent to participate in the study.

### 2.2. Data Collection

Patients who gave consent to the study underwent interviews using a standardized questionnaire used to capture data on socio-demographic and clinical characteristics (including smoking, alcohol and caffeine containing beverages use and diabetes treatment history).

Participants were also evaluated for signs and symptoms of DCAN including resting tachycardia, exercise intolerance, orthostatic hypotension (OH) (dizziness, light headedness, presyncope and syncope), abnormal blood pressure (BP) regulation, SMI and ischemia [12].

All study participants were subjected to an ECG event recorder performed by the research doctor or research assistant using an ECG machine (We cardio UN). All the ECG results were read by the research doctor.

DCAN diagnosis was made using Ewing's and San Antonia consensus panel for diagnosis, involving 5 Cardiovascular Reflex tests (CARTs). Blood pressure (BP) from the right arm using an ambulatory blood pressure monitor after subjects had rested for at least 10 minutes. BP was measured in a sitting or a supine position every minute for 3 minutes and recorded, then the subject was asked to change position to erect or standing position, BP was measured every minute for 5 minutes and recorded. Postural Hypotension was defined as a fall in systolic blood pressure (SBP) of  $\geq 30$  mmHg or DBP of  $\geq 10$  mmHg. Diastolic BP (DBP) response to handgrip was measured by asking the patient to squeeze a dynamometer to a maximum and maintain at 30% maximum for 5 minutes and DBP was measured and recorded. An abnormal test was a rise in DBP  $\leq 10$  mmHg.

Participants heart rate (HR) was measured and recorded. Resting Tachycardia

was defined as rate of >100 beats per minute (bpm). HR was calculated as a 30:15 ratio (postural Index). Whereas, the patient was connected to an ECG event recorder while lying down, then stood to a full upright position while ECG was recording for 180 seconds. The maximum/minimum 30:15 ratio was the longest RR interval between beats 14 - 20 divided by the shortest RR interval between beats 5 - 25, postural Index <1.0 was considered as abnormal. In Addition, HR variability was measured during deep breathing while the patient was lying down. The patient was asked to take 6 deep breaths per minute (that is 6 seconds of deep slow inspiration followed by 4 seconds of expiration). The ratio of maximum and minimum RR interval during expiration (E) and Inspiration (I) was calculated.  $E: I \leq 1.11$  was considered abnormal. Furthermore, Valsalva maneuver was carried out. While in a supine position with the nose closed, the patient was asked to breath into a mouth piece to a maximum of 40mmHg for 15 seconds, then the patient was asked to breath regularly with removal of pressure for another 15 seconds. During this time, the HR was recorded on an ECG event recorder and RR interval ratio (ratio of the longest RR interval to the shortest RR interval following the pressure release) was calculated and recorded. Abnormal results were ratio <1.2. Conclusively, DCAN diagnosis was based on 2 or more abnormal CARTs.

Peripheral/other neuropathy was defined as a self-reporting burning sensation or numbness, erectile dysfunction and decreased libido in absence of other medical conditions documented or formally diagnosed.

### 2.3. Data Analysis

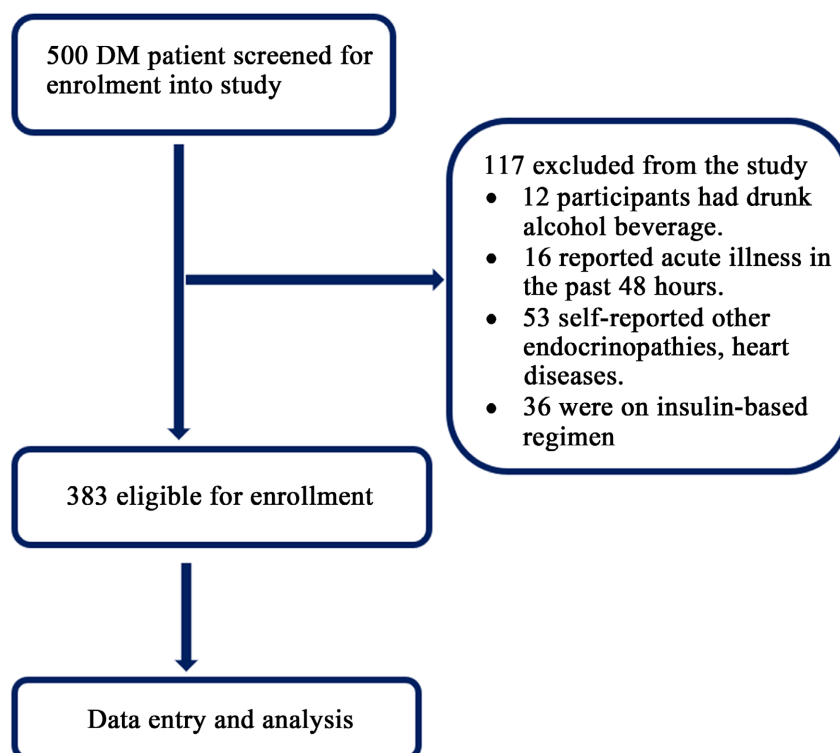
Data from questionnaire was verified and entered into Microsoft Excel and cleaned. STATA version 15 was used for data cleaning, checking for inconsistency or missing values, variables transformation, generating, recording variables, duplicate entries or any unusual values (outliers) were identified and removed prior analysis. Continuous variables were summarized appropriately using mean with standard deviation or median with the interquartile range depending on the distribution. Shapiro Wilk W test was used to check if the continuous variables were normally distributed or not.

Categorical variables were summarized using frequency and proportion (percent). DCAN associated factors were evaluated using binary logistic regression analysis. Any factor with a P value less than 0.05 by univariate analysis was further analyzed by multivariate logistic regression through forward stepwise selection.

## 3. Results

### 3.1. Enrollment

During the study period from June 2022 to November 2022, a total of 500 diabetic patients at Bugando Medical Centre (BMC) in Mwanza Region were screened for enrolment. Among the screened, patients 383 were eligible for the study, 117 candidates did not meet the inclusion criteria (**Figure 1**).



**Figure 1.** Enrolment flow chart.

### 3.2. Baseline Social Demographic Data

This study enrolled 383 Dm patients. The median age was 57 [IQR: 52 - 56]. Among the study patients, 37.2% (145) were males and 62.8% (240) were females. Other characteristics are described in **Table 1**.

**Table 1.** Baseline socio-demographic data (n = 383).

Characteristic	Number (%)	Percentage (%)
<b>Gender</b>		
Males	145	37.9
Females	240	62.1
<b>Age (years)</b>		
18 - 39 years	41	10.7
40 - 59 years	204	43.3
≥60 years	138	36.0
<b>Marital status</b>		
Single	2	0.5
Married	318	83
Divorced/separated/widowed	63	16.5

**Continued****Level of education**

No formal education	26	6.8
Primary school education	234	61.1
Secondary education	68	17.8
Post-secondary and higher education	55	14.4

**Source of income**

Farmer/peasant	216	56.4
Petty trader/manual workers	85	22.2
Professional/business	57	14.9
No formal employment	25	6.5

**3.3. Baseline Clinical Characteristics of Study Participants**

The median duration of diabetes Meletus was 7 [IQR: 3 - 12]. Among 383 Dm patients 77.4% (258) were also hypertensive, with 25.6% (98) having HTN diagnosis for at least 10 years and a median of 3 [IQR: 0 - 10]. Among the study participants, 40.2% (154) reported presence of peripheral neuropathy. Other characteristics are as described in **Table 2**.

**Table 2.** Baseline clinical characteristics of enrolled patients (n = 383).

Characteristic	Number (n)	Percentage (%)
<b>Duration of diabetes</b>		
0 - 4 years	132	34.5
5 - 9 years	99	25.9
≥10 years	152	39.7
<b>Hypertension</b>		
HTN absent	125	32.6
HTN present	258	77.4
<b>HTN duration</b>		
0 - 4 years	92	24.0
5 - 9 years	68	17.8
≥10 years	98	25.6
<b>Peripheral neuropathy</b>		
Present	154	40.2
Absent	229	59.8

**Continued****Other neuropathy**

Present	132	34.5
Absent	251	65.5

**Resting tachycardia**

Present	76	20.2
Absent	301	79.8

**Postural hypotension**

Present	92	24.0
Absent	291	76.0

### 3.4. Baseline Physical and Laboratory Characteristics of Study Participants

Majority of the study participants were overweight 43.9% (168) median BMI of 26.4 [IQR: 24.0 - 29.1]. Moreover, of 383 participants, 50.4% (193) had poorly controlled DM with median HbA1c of 6.9 [IQR: 6.4 - 8.7]. Moreover, majority of the study participants had one or more derangements in their lipid profiles. **Table 3** shows more details on baseline physical and laboratory characteristics of the participants.

**Table 3.** Baseline physical and laboratory characteristics (n = 383).

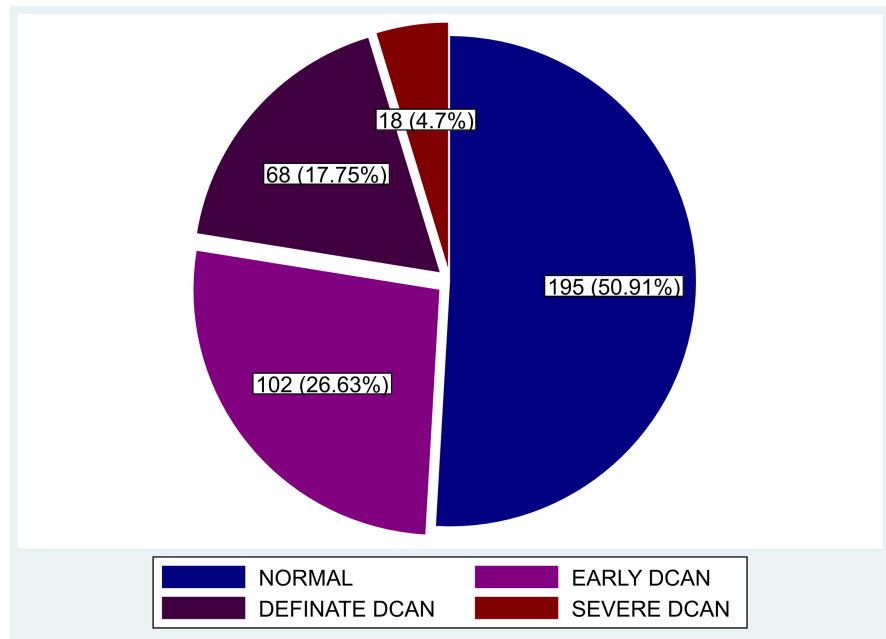
Variable	Number (n)	Percentage (%)
<b>HbA1C</b>		
Controlled ( $\leq 7\%$ )	190	49.6
Poorly controlled ( $> 7\%$ )	193	50.4
<b>Total cholesterol</b>		
Normal ( $\leq 5.2$ mmol/l)	190	49.6
Abnormal ( $> 5.2$ mmol/l)	193	50.4
<b>High Density Lipoprotein (HDL)</b>		
Normal ( $\geq 1$ mmol/l)	190	49.6
Abnormal ( $< 1$ mmol/l)	193	40.4
<b>Low Density Lipoprotein (LDL)</b>		
Normal ( $\leq 3.4$ mmol/l)	164	42.8
Abnormal ( $> 3.4$ mmol/l)	219	57.2
<b>Serum triglycerides</b>		
Normal ( $\leq 1.7$ mmol/l)	190	49.6
Abnormal ( $> 1.7$ mmol/l)	193	50.4

### 3.5. DCAN Diagnosis and Prevalence

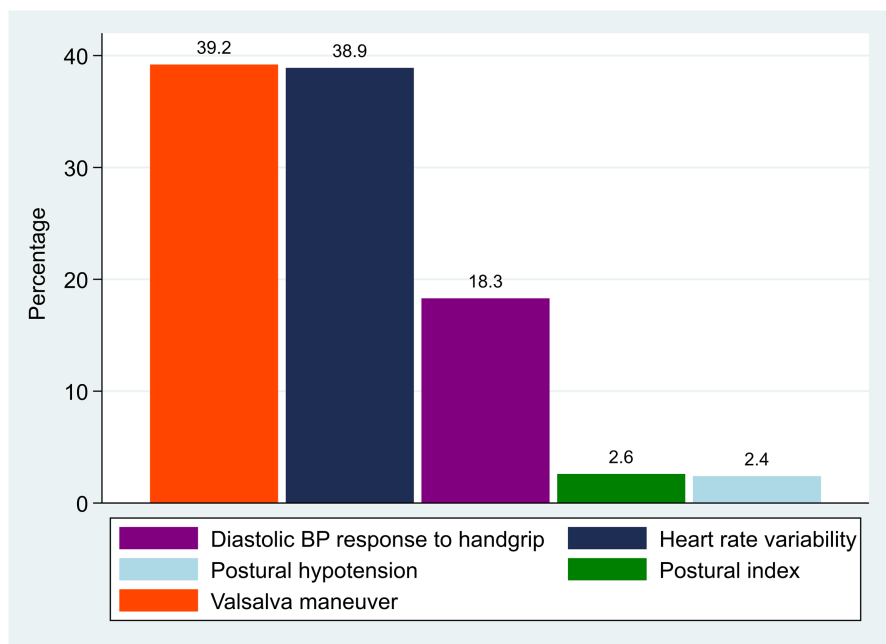
DCAN was observed in 49.1% (188) of the 383 patients, with 26.6% (102) having early DCAN and 4.7% (18) having severe DCAN. Abnormal postural Index was observed less 2.6% (10) compared to Valsalva Maneuver 39.2% (150). Other characteristics are shown in **Table 4**. **Figure 2** shows DCAN distribution among DM population and **Figure 3** shows distribution of abnormal CARTs in the study population.

**Table 4.** DCAN diagnosis and prevalence (n = 383).

DCAN characteristics	Number (%)	Percentage (%)
<b>Postural Index (PI)</b>		
Normal ( $\geq 1.04$ )	274	64.5
Borderline (1.03 - 1.01)	126	32.9
Abnormal ( $\leq 1.00$ )	10	2.6
<b>Valsalva Maneuver (VM)</b>		
Normal ( $\geq 1.21$ )	163	42.6
Borderline (1.20 - 1.11)	70	18.3
Abnormal ( $\leq 1.00$ )	150	39.2
<b>HR variability (E: I)</b>		
Normal ( $\geq 1.21$ )	148	38.6
Borderline (1.20 - 1.11)	86	22.5
Abnormal ( $\leq 1.00$ )	149	38.9
<b>Diastolic BP response to handgrip</b>		
Normal ( $\geq 15$ mmHg)	161	42.0
Borderline (15 - 11 mmHg)	152	39.7
Abnormal ( $\leq 10$ mmHg)	70	18.3
<b>Postural hypotension</b>		
Normal (SBP $\leq 11$ mmHg)	365	95.3
Borderline (SBP 11 - 29 mmHg)	9	2.4
Abnormal (SBP $\geq 30$ /DBP $\geq 10$ mmHg)	9	2.4
<b>DCAN prevalence</b>		
Normal	195	50.9
Early DCAN	102	26.6
Definite DCAN	68	17.8
Severe DCAN	18	4.7



**Figure 2.** DCAN distribution among DM study participants (n = 383).



**Figure 3.** Distribution of abnormal CARTs in the study population (n = 383).

### 3.6. Factors Associated with Diabetic Cardiac Autonomic Neuropathy

Following univariate logistic regression, the factors associated with Diabetic Cardiac Autonomic Neuropathy (DCAN) in the study population were age greater than 60 years (OR: 2.30; 95% CI: 1.55 - 6.82; p-value = 0.002), duration of DM  $\geq$  5 - 9 years (OR: 3.43; 95% CI: 1.10 - 3.21; p-value = 0.021) and a duration of more than 10 years (OR: 3.43; 95% CI: 2.10 - 5.95; p-value < 0.001). Co-morbidities that

were further associated with DCAN were presence of hypertension for more than 10 years (OR: 2.29; 95% CI: 1.33 - 3.95; p-value < 0.003), peripheral neuropathy (OR: 2.58; 95% CI: 1.69 - 3.93; p-value < 0.001). Moreover, physical and clinical characteristics that were associated with DCAN were a higher BMI of more than 30 (OR: 0.82; 95% CI: 2.73 - 5.59.1; p value < 0.01) and poorly controlled DM with HbA1C more than 7% (OR: 2.51; 95% CI: 1.58 - 3.66; p-value < 0.001).

Following multivariate analysis pathological Q (OR: 2.74; 95% CI: 1.21 - 6.23; p-value < 0.016), BMI more than 30 (OR: 1.41; 95% CI: 1.17 - 1.69; p-value < 0.001) and presence of resting Tachycardia (OR: 2.87; 95% CI: 1.65 - 4.99; p-value < 0.001) were significantly associated with DCAN. Age more than 60 years peripheral neuropathy, postural hypotension, elevated triglycerides, LDL and reduced HDL and hypertension and Dm duration though significantly associated with DCAN, were not analyzed by multivariate analysis due to collinearity with BMI, presence of resting tachycardia and pathological Q wave. Other findings are as shown in **Table 5**.

**Table 5.** Factors associated with DCAN among study participants (n = 383).

Variable	No Dcan (%)	Dcan (%)	Univariate		Multivariate	
			OR [95% CI]	p-value	OR [95% CI]	p-value
<b>Gender</b>						
Males	25 (6)	71 (19)	Ref			
Females	43 (11)	127 (33)	0.96 (0.63 - 1.45)	0.862		
<b>Age</b>						
18 - 39 years	28 (7.3)	13 (3.4)	Ref			
40 - 59 years	112 (29.2)	92 (24.0)	1.77 (0.86 - 3.61)	0.117		
≥60 years	55 (14.4)	83 (21.7)	3.27 (1.55 - 6.82)	<b>0.002</b>	<b>-*</b>	<b>-*</b>
<b>Marital status</b>						
Single	1 (0.3%)	1 (0.3)	Ref			
Married	163 (42.6)	155 (40.5)	0.95 (0.06 - 15.33)	0.972		
Divorced/separated/widowed	31 (8.1)	32 (8.4)	1.03 (0.06 - 17.23)	0.982		
<b>Education level</b>						
No formal education	15 (3.9)	11 (2.9)	Ref			
Primary school education	111 (29.0)	123 (32.1)	1.51 (0.67 - 3.43)	0.323		
Secondary education	39 (10.2)	29 (7.6)	1.01 (0.41 - 2.53)	0.976		
Post-secondary and higher education	30 (7.8)	25 (6.5)	1.14 (0.44 - 2.91)	0.790		

**Continued****Source of income**

Farmer/peasant	107 (27.9)	109 (28.5)	Ref		
manual workers	40 (10.4)	45 (11.8)	1.10 (0.67 - 1.83)	0.699	
Professional	33 (8.6)	24 (6.3)	0.71 (0.40 - 1.29)	0.263	
No formal employment	15 (3.9)	10 (2.6)	0.65 (0.28 - 1.52)	0.325	

**DM duration**

0 - 4 years	88 (23)	44 (11.5)	Ref		
5 - 9 years	51 (13.3)	48 (12.5)	1.88 (1.10 - 3.21)	<b>0.021</b>	1.49 (0.83 - 2.69) 0.186
≥ 10 years	56 (14.6)	96 (25.1)	3.43 (2.10 - 5.59)	<b>&lt;0.001</b>	<b>-*</b> <b>-*</b>

**HTN duration**

0 - 4 years	56 (14.6)	36 (9.4)	Ref		
5 - 9 years	34 (8.9)	34 (8.9)	1.27 (0.70 - 2.30)	0.45	
≥10 years	35 (9.1)	63 (16.5)	2.29 (1.33 - 3.95)	<b>0.003</b>	<b>-*</b> <b>-*</b>

**Peripheral neuropathy**

Absent	138 (36)	91 (23.8)	Ref		
Present	57 (14.9)	97 (25.3)	2.58 (1.69 - 3.93)	<b>&lt;0.001</b>	<b>-*</b> <b>-*</b>

**Other neuropathy**

Absent	134 (35)	117 (30)	Ref		
Present	61 (15.9)	71 (18.5)	1.33 (0.87 - 2.03)	0.182	

**Resting tachycardia**

Absent	167 (44.3)	134 (35.5)	Ref		
Present	23 (6.1)	53 (14.1)	2.87 (1.67 - 4.93)	<b>&lt;0.001</b>	2.87 (1.65 - 4.99) <b>&lt;0.001</b>

**Postural hypotension**

Absent	163 (42.6)	128 (33.4)	Ref		
Present	32 (8.4)	60 (15.7)	2.39 (1.47 - 3.89)	<b>0.000</b>	<b>-*</b> <b>-*</b>

**BMI**

Normal weight (18.5 - 24.9)	83 (21.7)	49 (12.8)	Ref		
Overweight (25 - 29.9)	83 (21.7)	85 (22.2)	1.73 (1.09 - 2.76)	<b>0.020</b>	1.37 (0.83 - 2.27) 0.222
Obese (≥30)	29 (7.6)	54 (14.1)	3.15 (1.78 - 5.59)	<b>0.000</b>	2.27 (1.20 - 4.30) <b>&lt;0.001</b>

**Continued****HbA1C (%)**

Controlled ( $\leq 7$ )	136 (35.5)	92 (24.0)	Ref			
Poorly controlled ( $> 7$ )	59 (15.4)	96 (25.1)	2.91 (1.58 - 3.66)	<b>0.000</b>	<b>-*</b>	<b>-*</b>

**HDL (mmol/l)**

Normal ( $\geq 1$ )	130 (33.9)	60 (15.7)	Ref			
Abnormal ( $< 1$ )	65 (17)	128 (33.4)	4.27 (2.78 - 6.54)	<b>0.000</b>	<b>-*</b>	<b>-*</b>

**LDL (mmol/l)**

Normal ( $\leq 3.4$ )	117 (30.6)	47 (12.3)	Ref			
Abnormal ( $> 3.4$ )	78 (20.4)	141 (36.8)	4.50 (2.91 - 6.97)	<b>0.000</b>	<b>-*</b>	<b>-*</b>

**Triglycerides (mmol/l)**

Normal ( $\leq 1.7$ )	128 (33.4)	62 (16.2)	Ref			
Abnormal ( $> 1.7$ )	67 (17.5)	126 (32.9)	3.88 (2.54 - 5.93)	<b>0.000</b>	<b>-*</b>	<b>-*</b>

**Prolonged QTc**

Absent	39 (10.2)	20	Ref			
Present	14 (3.7)	27 (7.1)	2.17 (1.10 - 4.28)	<b>0.026</b>	<b>-*</b>	<b>-*</b>

**Pathological Q**

Absent			Ref			
Present	9 (2.4)	25 (6.5)	3.17 (1.44 - 6.99)	<b>0.004</b>	2.54 (1.21 - 6.23)	<b>0.016</b>

-\* not analyzed by multivariate analysis due to collinearity with BMI, pathological Q and resting Tachycardia.

## 4. Discussion

This study was conducted to evaluate the prevalence of Cardiac Autonomic Neuropathy, associated factors, its correlation with silent Myocardial Infarction and prolonged QTc interval among diabetic patients at Bugando medical Centre. Diabetic Cardiac Autonomic Neuropathy (DCAN) was observed in at least half of the enrolled participants in line with other studies where the prevalence ranged from 30% - 60%. To the best of our knowledge these results using CARTs as a diagnostic tool are the first in our settings, demonstrating a remarkably high rate of DCAN in the country, emphasizing the importance of further studying this preventable and morbid condition in this population. The analysis identified common cardiovascular risk factors among other factors to be significantly associated with DCAN.

Among 383 enrolled patients, 49.1% (188) had DCAN diagnosis on the basis of two or more cardiovascular autonomic reflex tests (CARTs) as per San Antonio

Consensus Panel for DCAN diagnosis. Abnormal heart rate response to deep breathing as measured by expiration inspiration ratio (E: I) was observed in more patients as compared to postural hypotension that was least observed. Such results are evidence that using one abnormal CARTs in diagnosis of DCAN would inevitably miss or overestimate some of the DCAN patients.

San Antonio Consensus Panel recommends that both parasympathetic and sympathetic functions should be evaluated independently. When analyzed separately pure parasympathetic (Postural Index, Valsalva maneuver, heart rate response to deep breathing) dysfunction was more commonly observed, while sympathetic (postural hypotension and diastolic BP in response to hand grip) dysfunction was less observed in the DCAN population. These results suggest that parasympathetic dysfunction is more common than sympathetic dysfunction and the later suggests a more severe disease in line with San Antonio Consensus Panel and Ewing's criteria [13] [14]. Similar findings were also observed in India, a study by Jawahar *et al.* [15], where DCAN prevalence was 52% with 52% having parasympathetic abnormalities vs 26% with sympathetic abnormalities.

The prevalence observed in this study is comparable to findings by Migisha *et al.* in Uganda 2020 where the prevalence was 52.2% [7] and from several other studies elsewhere in lower and middle-income countries (LMICs) that have reported prevalence between 42% and 63% [16]-[18]. These comparable results could be attributed to the similarity in the study population with majority of the patients having uncontrolled DM as well as the same diagnostic criteria used in the study. Likewise, a study by Moțățăianu *et al.* in Romania, 2018 showed a prevalence as low as 39.1% in T2DM and as high as 61.8% in T1DM patients, suggesting that longer DM duration in T1DM patients increases the odds of DCAN in that population [19]. Likewise, a cross-sectional hospital based study by Flora Ruhangisa *et al.* In Kilimanjaro, Tanzania revealed a lower prevalence of 32% [8] as compared to our study, this could have been attributed to the use of QTc interval prolongation as the only criteria for the diagnosis of DCAN and might have missed some DCAN patients.

In contrast, other studies have reported a prevalence as low as 1.8%. A study by Zoppin *et al.* in Italy, 2015 revealed a much lower prevalence of DCAN (1.8%), however, the study recruited newly diagnosed T2DM thus suggesting the difference in prevalence in comparison to our study, where majority of the patients had a DM duration of more than 5 years [20]. In another study by Kempler *et al.*, 2002 the prevalence of DCAN among T1DM patients was lower (36%) [21] compared to our study, this difference could have being attributed not only to the difference in the study population to our study but also the criteria used to diagnose DCAN, whereas, Kempler *et al.* only used two abnormal CARTs ( heart rate variability test and postural hypotension test) instead of the five tests recommended by the San Antonio consensus panel, thus missing some of the DCAN patients.

A study K. Jennifer *et al.*, reveled a much higher prevalence (87.2%) compared to our study [22], the study by Jennifer *et al.* used a cut off diagnostic criteria of

one abnormality in one of the CARTs which is different from our study, where two or more abnormalities in the CARTs had to be positive for DCAN diagnosis thus exaggerating DCAN diagnosis.

Regardless of whether the patient has T1DM or T2DM, the magnitude at which cardiac autonomic neuropathy impacts DM patients is still significantly high as observed in our study and many other studies, thus DM patients should be screened, informed and action taken to reduce its occurrence and associated morbidity and mortality.

#### **Factors associated with diabetic cardiac autonomic neuropathy.**

This study has revealed a significant association between DCAN and BMI of more than 30. Majority of our DCAN population were either overweight or obese 23% and 18% respectively. Overweight and obesity have been associated with increase insulin resistance contributing to the etiology of metabolic syndrome, progression and development of DCAN. Multiple other studies including a study by Mohamed Daaffala *et al.* have shown an association between a higher BMI and DCAN [23]. Findings from Muhanad M. Dhumad *et al.*, showed no association between DCAN and BMI [24] attributing the lack of association to the fact that BMI is a measure of adipocyte but not the distribution of fats throughout the body. A 2020 meta-analysis by Mitra Darbandi revealed that waist hip ratio to be better predictor for cardiovascular risk occurrence than BMI [25].

In this study, DCAN was significantly associated with pathological Q wave with a total of 8.8% (34) DM patients having a pathological Q wave out of 383 patients, 7.6% (29) having both pathological Q wave and DCAN compared to 1% (3) having pathological Q wave but without DCAN. In a Japanese study by Hirofumi Soejima *et al.*, 2018, silent MI as diagnosed by a pathological Q wave in a rest ECG among T2DM patients was 25% in all types of MIs in the study population [26]. In a study by Enayat Niakan, revealed a silent MI prevalence of 13.7% among adult DM patients as diagnosed by a pathological Q wave in a rest ECG, of which 20% had both DCAN and pathological Q wave [27]. These findings are comparable to our findings and illustrate an increase in silent MI not only among DM patients but even among DM patients with CAN, thus emphasizing on screening DM patients for possible CAD including silent MI even with a tool as simple as a rest ECG.

In the current study, resting tachycardia has been significantly associated with DCAN. Due to abnormalities in the parasympathetic and sympathetic function, resting tachycardia and postural hypotension have been some of the clinical manifestations of DCAN [28].

Patient's age, peripheral neuropathy, postural hypotension, dyslipidemia, HbA1C, hypertension duration and DM duration although statistically significant were deliberately omitted in the final model (multivariate analysis) because of multicollinearity with the above-mentioned factors.

Age greater than 60 years was associated with DCAN, attributed to the long duration of DM among elderly patients compared to young subjects. Advanced age is known to be associated with various changes in the autonomic system. These

changes include: a gradual increase in basal and stimulated plasma noradrenaline concentrations, altered adrenoceptor function and diminished responsiveness to adrenergic agonists [29], thus causing a decline in heart rate response to Valsalva maneuver (VM) and standing (PI) compared to younger subjects. This theory is also noted in our study where 20% of patients aged >60 years had an abnormal VM as compared to 9% of those aged ≤39 years, likewise with abnormal PI where 7% were aged >60 years and only 2% for those ≤39 years. A higher prevalence of DCAN associated with age in this study is similar to multiple other studies [30] [31]. A study by Eze *et al.*, with 70 enrolled patients and a mean age of 55.76 [±8.62 years) revealed a higher prevalence (50%) in participants aged more than 50 years compared to the younger population [32]. This similarity could be attributed to the multifactorial pathogenesis of DCAN, with older people more likely to have had a longer duration of DM, as well as older people even without DM are more likely to have insulin resistance which causes a reduction in cardiac autonomic dysfunction as stated by Anna K poon *et al.*, 2020 [33]. In contrast, a study by Ekta Khandelwal *et al.*, 2010 showed no association between patient's age and development or progression of DCAN [18], this difference from our study could be due to a younger population (mean age 45.36 ± 13.35) in the Ekta study as compared to our study.

A duration of 5 - 9 years and more than 10 years was associated with DCAN in our study. It is well established that T1DM tends to have a longer duration of the disease compared to T2DM thus leading to multiple DM associated complications including DCAN. However, most T2DM may have the disease earlier on before the diagnosis is made, predisposing them to prolonged hyperglycemia states that induced oxidative stress and toxic Advanced Glycosylation products that lead to changes in the mitochondrial functions and membrane permeability and endothelial functions [34] that cause neuronal damage and thus DCAN. With majority of study participants 152 (39.7%) of 383 having longer duration of DM and mean duration of 10 years, DCAN prevalence across the DM period among other factors is also likely to be high considering the pathophysiology stated above. In Northeast India, a study by Ashok K. Bhuyan with a mean DM duration of 9.03 ± 6.4 years revealed a significant association between DCAN and duration of DM [35].

Poorly controlled DM was significantly associated with DCAN. As stated above higher glycemic levels are associated with increased neuronal damage despite the type of DM. In the current study, 50% of the study participants had HbA1C > 7.0% with a mean HbA1C of 7.8, which is greater than the ADA 2021 recommendation of HbA1C < 7.0. These findings are similar to multiple other studies, A study by D.R Witte *et al.*, 2004 showed an increased risk of DCAN by 20% with per point increase of HbA1c [36]. However, Migisha *et al.* did not reveal such an association between glycemic control and DCAN [7], this difference could be because Migisha used fasting glucose as a measure of glycemic control instead of HbA1C which would reflect a short-term glycemic control.

Further association was noted in patients who had hypertension for more than 10 years. The exact mechanism showing an association between cardiac autonomic neuropathy and hypertension in diabetic patients has not been extensively studied, it is, however, proposed that abnormalities in the vagal activities lead to enhanced sympathetic activity thus causing hypertension among patients with abnormal CARTs [37]. In a study by Emily B *et al.*, 2003, there was an increase in the incident of hypertension preceded by abnormalities in heart rate variability tests 9 years prior to the diagnosis of hypertension [38], thus showing an association between hypertension duration and DCAN.

DCAN was also statistically significant in the population with peripheral neuropathy. This association was also noted in a study by K. Pafili in Greece, 2019, that evaluated the correlation between DCAN and peripheral neuropathy where both parasympathetic and sympathetic dysfunctions were associated with peripheral neuropathy [39]. Contrary to our study, a study by N.Tentolouis in 2001 found no association between DCAN and peripheral neuropathy [40].

The exact mechanism of how dyslipidemia is associated with DCAN is unknown, it is, however, proposed that enhanced oxidative stress in DM patients contributes to neuronal damage as seen in a study by Andrea *et al.* [41]. This study has shown an association between DCAN and dyslipidemia (abnormal total cholesterol, HDL, LDL and Triglycerides). These findings are similar to a study by Lige Song *et al.* in China 2016, where DCAN was associated with dyslipidemia especially high Triglyceride levels, and there was no correlation between DCAN and HDL [42]. Opposed to our study, findings from a meta-analysis by Mohamed Dafaalla *et al.*, showed no association between lipid abnormalities and DCAN [23].

Other socio-demographic data like sex, level of education and marital status were not associated with DCAN, neither was presence or absence of other neuropathies.

A total of 41 (11%) DM patients had prolonged QTc interval among which only 32 (8%) had both DCAN and prolonged QTc interval vs 166 (43%) that had DCAN but not prolonged QTc interval, and 65 (17%) having neither DCAN nor prolonged QTc interval. This study results are similar from the study by Ogba Ukpabi *et al.*, in Nigeria [43]. Our results are different from a study by K. Jennifer *et al.* where there was no association between DCAN and prolonged QTc interval [22].

## 5. Conclusion

DCAN is prevalent among DM patients attending medical outpatient clinic at BMC. Obesity and prolonged QTc interval are identified factors associated with DCAN, measures should be taken to address the increase in obesity in our population as well as a rest ECG should be performed more often in diabetic patients more so DCAN patients to address the grave clinical repercussion associated with pathological Q wave.

## 6. Recommendation

Following the study findings and observations, below are some of the recommendations:

- 1) All DM patients should be screened for Cardiac autonomic neuropathy at least annually for low-risk patients;
- 2) Emphasis should be put on diet and physical activity to reduce the burden of obesity among DM population;
- 3) A cohort study should be conducted after application of preventive measures e.g. weight reduction, blood glucose control so as to have evidence based management of DCAN.

## Ethical Approval

Ethical clearance for this study was sought from the Joint BMC/CUHAS Ethics review committee. Permission to conduct this study was also sought from Bugando Medical Centre. Participants were requested to sign a consent form for their willingness to participate in the study. For participants unable to sign or write, a thumbprint was requested. The benefit of the study was explained to patients or caregivers before they gave consent to participate in the study. Those who declined to participate were still entitled to all usual care. All results were given to patients and attending clinicians. Confidentiality was highly maintained and results were made available in patient's file immediately after screening.

## Availability of Data and Materials

Data set used for this study is not publicly available so as maintain participant's confidentiality. On reasonable request, data may be made available from the corresponding author.

## Authors Contributions

SSK, SM an EM conceptualized and designed the study, performed data analysis, interpreted the results and wrote the manuscript

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## Conflicts of Interest

We declare no conflict of interest.

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## List of Abbreviation

<b>BMI</b>	Body Mass Index.
<b>BP</b>	Blood Pressure.
<b>SBP</b>	Systolic Blood Pressure.
<b>DBP</b>	Diastolic Blood Pressure.
<b>CARTs</b>	Cardiac Autonomic Reflex Tests.
<b>CVD</b>	Cardiovascular Diseases.
<b>DCAN</b>	Diabetic Cardiac Autonomic Neuropathy.
<b>CAN</b>	Cardiac Autonomic Neuropathy.
<b>DM</b>	Diabetes Mellitus.
<b>ECG</b>	electrocardiogram.
<b>FBG</b>	Fasting Blood Glucose.
<b>HbA1C</b>	Glycosylated Hemoglobin.
<b>HDL</b>	High Density Lipoprotein.
<b>QTc</b>	corrected QT interval.
<b>MOPD</b>	Medical Outpatient Department
<b>HR</b>	Heart Rate.
<b>HTN</b>	Hypertension.
<b>LDL</b>	Low Density Lipoprotein.
<b>MI</b>	Myocardial Infarction.
<b>ms</b>	millisecond.
<b>PI</b>	Postural Index.
<b>PR</b>	Pulse Rate.
<b>SMI</b>	Silent myocardial infarction.
<b>T1DM</b>	Type 1 Diabetes Mellitus.
<b>T2DM</b>	Type 2 Diabetes Mellitus.
<b>UDM</b>	Undiagnosed DM.
<b>ECHO</b>	Echocardiogram.
<b>NADP</b>	Nicotinamide Adenine Dinucleotide Phosphate.
<b>NADPH</b>	Nicotinamide Adenine Dinucleotide Phosphate hydrogen.