Open Access Library Journal
2024, Volume 11, e11747
ISSN Online: 2333-9721
ISSN Print: 2333-9705

Common Factors Associated with Diabetic Cardiac Autonomic Neuropathy (DCAN); Patterns and Their Percentages among Diabetic Patients Diagnosed to Have Cardiac Autonomic Neuropathy in Bugando Zonal Referral Hospital in Mwanza, Western Zone of Tanzania

Mosses Simon[1*], Sabrina S. Kumlin[2], Bantar Tawe[3], Isaack Ajee[4]

[1]Medical Section, United Nations (UN), Mazar-e-Sharif, Afghanistan
[2]Department Internal Medicine, Bugando Medical Centre (BMC), Mwanza, Tanzania
[3]Medical Section, United Nations (UN), Kabul, Afghanistan
[4]Obsy/Gynaecology Department, Geita Regional Refferal Hospital (GRRH), Geita, Tanzania
Email: *mossessimon89@gmail.com

How to cite this paper: Simon, M., Kumlin, S.S., Tawe, B. and Ajee, I. (2024) Common Factors Associated with Diabetic Cardiac Autonomic Neuropathy (DCAN); Patterns and Their Percentages among Diabetic Patients Diagnosed to Have Cardiac Autonomic Neuropathy in Bugando Zonal Referral Hospital in Mwanza, Western Zone of Tanzania. *Open Access Library Journal*, **11**: e11747.
https://doi.org/10.4236/oalib.1111747

Received: May 27, 2024
Accepted: July 28, 2024
Published: July 31, 2024

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 and other factors have been associated with the development and progression of DCAN. This study was conducted to evaluate the common DCAN-associated risk factors and their percentages in diabetic patients to help clinical and public health practitioners address and tackle the problem of treatment and preventive measures to be established to reduce that life-threatening diabetic complication, *i.e.*, DCAN. **Objectives:** To determine the Common factors associated with Diabetic Cardiac Autonomic Neuropathy (DCAN); Patterns and their percentages among Diabetic patients diagnosed to have Cardiac Autonomic Neuropathy in Bugando Zonal Referral Hospital in Mwanza, Western zone of Tanzania. **Methodology:** A hospital-based cross-sectional study was conducted in the DM MOPD at BMC, with a sample size of 188 DCAN patients. A standard questionnaire was used for Data collection and summarized in a common Excel sheet. Data were analyzed using STATA version 15, DCAN associated factors were analyzed using bivariate logistic regression models. **Results:** Out of 188 patients with DCAN,

Heart rate variability was the most common abnormality 38.9% (149) and Postural hypotension was the least 2.4% (9) among DCAN patients. Nevertheless, Obesity and resting tachycardia were significantly associated with DCAN. Though statistically significant, Age, HbA1C, dyslipidemia, hypertension, and DM duration were not analyzed in the final model because of collinearity with BMI and resting tachycardia. **Conclusion:** Resting Tachycardia, more than 10 years of Diabetic Miletus (DM), more than 10 years of Hypertension, age above 60 years, and hyperlipidemia, poorly controlled DM with HbA1C more than 7% were statistically found to be associated with DCAN development among DM patients. Immediately measures should be taken to address the situation, and most of them can be prevented and controlled with clinical or public health interventions to rescue DM patients against this life-threatening complication (DCAN) in communities at large.

Subject Areas

Diabetes, Endocrinology

Keywords

DCAN, BMI, DM

1. Introduction

The prevalence of Diabetes Mellitus (DM) is increasing globally in both resource-rich and resource-limited countries, including Sub-Saharan Africa (SSA). The increase in DM prevalence could partly be attributed to urbanization, an increase in life expectancy, and improved diagnosis rates of DM [1]. According to the International Diabetes Federation (IDF), in 2020, the global DM prevalence was 463 million, with more than 19 million people in Africa.

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 DM set after excluding other causes [2]. Globally, the prevalence of DCAN ranges from 1% - 90% in type 1 DM (T1DM) and 20% - 73% in type 2 DM (T2DM), with a predicted annual increment of 1.8% in patients with well-controlled DM [3]. This wide variation could be attributed to the inconsistent diagnostic criteria used for the diagnosis of DCAN throughout the studies.

In Africa, especially Sab Saharan Africa there are limited numbers of studies on DCAN. Migisha *et al.* in Uganda reported a DCAN prevalence of 52.2% [4]. DCAN, when present, is mainly irreversible, hence, screening and identifying associated potentially modifiable risk factors is very crucial, especially for low-income countries. The main risk factors that are known to be associated with DCAN are increasing age, longer duration of diabetes since diagnosis, poor glycemic control, and increased body mass index [4]. However, data in Tanzania

on DCAN-associated risk factors and their percentages in diabetic patients is scanty, hence difficulties in implementing prevention, modification, and treatment plans. This study will evaluate the common DCAN-associated risk factors and their percentages in diabetic patients with the aim to help clinical and public health practitioners address and tackle the problem of treatment and preventive measures to be established to reduce that life-threatening diabetic complication (DCAN).

1.1. Problem Statement

Cardiac autonomic neuropathy (CAN) is among the serious complications of DM, affecting multiple organ systems and is a major cause of morbidity and mortality in patients with DM, and is strongly associated with approximately five-fold increased risk of cardiovascular mortality. If no action is taken to prevent its development or progression, CAN is associated with major clinical repercussions such as sudden cardiac death attributed to silent myocardial infarction and arrhythmias. [5]

Despite a high global prevalence of DCAN 30% - 60% and an annual increment of 6% and 2% in T1DM and T2DM respectively [6], DCAN has not extensively being studied in African regions, including Tanzania. In a study by Migisha *et al.*, Uganda 2020, DCAN prevalence was estimated at 52.2%, associated with poor glycemic control, long duration of DM disease, retinopathy, and other traditional cardiovascular risk factors [7]. Despite the burden of DCAN being high among DM patients, the associated risk factors are not or less established in Mwanza, and Tanzania at large, and this situation closes the doors for Clinical and public health communities to develop interventions to prevent or reduce DCAN in DM patients.

1.2. Rationale

In a health resource-limited setting like Tanzania, which is affected by numerous infectious diseases and emerging Non-Communicable Diseases (NCD) including DM, the presence of DCAN is another burden that presses the overwhelmed healthcare system in operation, resulting in the increase of morbidity and mortality. Findings from this study will establish the existing risk factors associated with DCAN, hence promoting the Clinical and public Health departments to develop several interventions to prevent or reduce the burden of DCAN threats to the life of DM patients in the communities.

1.3. Objectives

1.3.1. Broad Objective

To determine the Common factors associated with Diabetic Cardiac Autonomic Neuropathy (DCAN); Patterns and their percentages among Diabetic patients diagnosed to have Cardiac Autonomic Neuropathy in Bugando Zonal Referral Hospital in Mwanza, Western zone of Tanzania.

1.3.2. Specific Objectives

- To determine the common factors associated with diabetic Cardiac Autonomic neuropathy.
- To determine the leading factors (in percentages) that are associated with diabetic Cardiac neuropathy.
- To address the burden of Diabetic Cardiac Autonomic Neuropathy associated factors to the clinician and public health practitioners for them to develop preventive measures/strategies to protect the diabetic community.

2. Literature Review

DM is among the most common Non-Communicable Diseases (NCD), rising during rapid population growth, increase in lifespan, urbanization, and increasing prevalence of obesity and physical inactivity [7]. Globally, the incidence and prevalence of DM have drastically increased by 102.9% from 1990 to 2017, with DM prevalence of 11.3 million people to 22.9 million people, respectively [8].

According to the International Diabetes Federation (IDF) in 2020, the global prevalence of DM was 463 million, and more than 19 million people in the African region. Sub-Saharan Africa is believed to have the highest proportion of undiagnosed diabetes, with more than two-thirds of people with diabetes unaware of their status. By 2045, the burden of SSA is estimated at 47 million people [8] [9].

Multiple studies conducted in Tanzania in different regions have shown variations in the prevalence of DM. Population-based studies done in Kilimanjaro and Mwanza regions documented the prevalence of DM to be 5.7% and 11.9% respectively, this is not so different from a hospital-based study done in Morogoro Regional Hospital which observed a DM prevalence of 10.08%. With an increase in prevalence and longer duration of DM in patients, DM complications, including DCAN, are only expected to take a toll in society as well as healthcare facilities if no emergent action is taken [10].

2.1. Overview of Diabetic Cardiac Autonomic Neuropathy (DCAN)

DCAN is a serious Macrovascular complication of DM, affecting multiple organ systems and a major cause of morbidity and mortality in patients with DM and strongly associated with an approximately five-fold increased risk of cardiovascular mortality. Based on the Subcommittee of the Toronto Consensus Panel on Diabetic Neuropathy, DCAN is defined as the impairment of cardiovascular autonomic control in the setting of DM after the exclusion of other causes. [11]

The San Antonio conference on DM neuropathy, in 1988, agreed upon a criterion for DCAN diagnosis that was both sensitive and specific once the parameters were used together. The Diagnosis of DCAN was made based on: A) The three tests recommended were heart rate response to 1) deep breathing, 2) standing, and 3) the Valsalva maneuver. B) Two tests of blood pressure control are recommended: blood pressure response to 1) standing or passive tilting and 2) sustained handgrip [12]. Cardiovascular Autonomic Reflex Tests (CARTs)

allow DCAN staging from early to advanced involvement. Progressive stages of DCAN are associated with an increasingly worse prognosis. Resting tachycardia is one of the earliest presentations of DCAN, while orthostatic hypotension is associated with advanced stages with an increase in the 10-year mortality rate. [13]

The prevalence of DCAN has been varying across the world. In a study by Anca *et al.* in Romania in 2018 the prevalence of DCAN was 61.8% and 39.1% in T1DM and T2DM respectively. Similarly, in a study by Valensi *et al.* in France 2003, the prevalence of DCAN among T1DM patients was higher by 18.2% than in T2DM 12.3 owing to the longer duration of DM in T1DM [14]. In a community cohort study by Ying Xue *et al.* between 2011 and 2013, DCAN prevalence was 29.1%. If no measures are taken to prevent or manage DCAN, it is estimated to have an annual increment of approximately 6% and 2% in patients with T1DM and T2DM respectively. [14]

In Africa, there is a study conducted in Nigeria in 2008 and 2013 among T2DM, DCAN prevalence was 34.2% and 44.3% respectively. The available study is from East Africa, Uganda in 2020 by Migisha *et al.*, where the prevalence of DCAN was 52.2%. [15]

2.2. Associated Factors of DCAN

Diabetic Cardiac Autonomic Neuropathy (DCAN) is a common and severe complication of diabetes that affects the autonomic nervous system, specifically the heart. The clinical characteristics of patients with DCAN often include a range of symptoms and findings: Cardiovascular Symptoms Resting Tachycardia: An increased resting heart rate (> 90 beats per minute). Orthostatic Hypotension is a significant drop in blood pressure upon standing, leading to dizziness, lightheadedness, or fainting. Exercise Intolerance reduces the ability to exercise, often accompanied by fatigue and shortness of breath. [15]

Gastrointestinal symptoms like gastroparesis include gastric emptying, which causes nausea, vomiting, bloating, and early satiety. Diarrhea or Constipation: Irregular bowel movements, often alternating between diarrhea and constipation. Genitourinary Symptoms Bladder Dysfunction: Difficulty emptying, leading to urinary retention or incontinence. Sexual Dysfunction like Erectile dysfunction in men and decreased sexual desire in women. Sweat Gland Dysfunction Anhidrosis: Reduced ability to sweat, especially in the extremities. Hyperhidrosis: Excessive sweating, particularly on the face and trunk. Other Autonomic Symptoms: Hypoglycemia Unawareness: Reduced ability to recognize the symptoms of low blood sugar. Pupillary Abnormalities: Abnormal pupil reactions affecting vision in low light conditions. [15]

Most published studies have documented poor glycemic controls, long duration of DM, age, and traditional Cardiovascular Risk Factors (CVRF) (Arterial hypertension, obesity, and dyslipidemia) to be key associated factors for the development and progression of DCAN [16]. This was also true in a hospital-based study done in Uganda in 2020 among DM patients by Migisha *et al.* [16]

In a population-based study KORA S4 survey (aged between 55 and 74 years) done in Augsburg-German, which aimed at determining the prevalence of DCAN in different degrees of glucose intolerance, found that the prevalence of DCAN is highest in individuals with known DM (17.5%) then newly diagnosed DM (11.7%), which is also higher than impaired fasting glucose (FG)+ impaired glucose tolerance (IGT) (11.4%), these values were still higher than isolated iFG (8.1%) and iGT (5.9%) and much less in normal glucose tolerance test (NGT) 4.5% [16]. These findings show the contribution of impaired glucose tolerance in the pathogenesis of DCAN even in patients who have not developed DM yet [17].

The Diabetic Control and Complications Trial (DCCT) in T1DM patients demonstrated that strict glycemic control, intensive DM treatment, and good metabolic control reduced the incidence of DCAN by 53% and slowed its progression. A follow-up study, Epidemiology of Diabetes Interventions and Complications Study confirmed the benefits of strict Glycemic control in prevention and slowing the progression of DCAN in a period of at least 8 years [17].

In T2DM patients, strict glycemic control is controversial, data from STENO-2 suggest that intensive Glycemic control and modification of CVRF reduced DCAN prevalence by 60%. Moreover, in the UK prospective diabetes study (UKPDS) glycemic control and traditional CVRF 12 especially blood pressure control were equally significant in the reduction and prevention of microvascular and macrovascular including DCAN progression among T2DM [18].

In a meta-analysis by Dafaalla *et al.* in 2016, there was a significant association of DCAN with advanced age, long duration of DM, high serum triglycerides, hypertension, and higher BMI among other risk factors. The risk for the development and progression of DCAN in T2DM patients is associated with traditional cardiovascular risk factors, including dyslipidemia. In a Chinese study by Lige Song *et al.* in 2016, the prevalence of DCAN in patients with high triglyceride levels was higher than in the group with low Triglyceride levels (35.25% vs 26.54%). However, this difference was not witnessed in other lipid profile parameters (HDL, LDL) [18].

Hypertension among T2DM patients plays a role in DCAN pathogenesis. One of the proposed theories is that DCAN is caused by an overt increased sympathetic tone and a defect in the vagal activity, hence this may also contribute to hypertension. In a study by F. Ayad *et al.* in Algeria, in 2010, the prevalence of hypertension among DCAN patients in T2DM was twice as high 16.3% compared to T1DM 8% [17] [18].

DCAN remains largely underdiagnosed and an overlooked complication of DM, despite its detrimental effects among DM patients worldwide. The most typical clinical evidence of DCAN in patients with concomitant CAD (coronary artery disease) is silent myocardial infarction. Chest pain is usually an alarming symptom for both patients and clinicians with suspicion of acute coronary syndrome [17]. However, in patients with DCAN, the failure to appreciate pain has an important clinical implication in patients with coronary artery diseases. Thus, most patients with DCAN and silent myocardial infarction might present with

ECG features of an old infarction (pathological Q wave). In a study by Gautam G. Lalani *et al.* in 2008, ECG Q wave defined by classic criteria accurately identifies post-infarct scar [17].

DCAN is associated with sudden cardiac death in multiple types of research, as noted above. Besides ischemic cardiac changes in DCAN, prolongation of QTc interval may predispose DCAN patients to life-threatening arrhythmias and sudden death. The prevalence of QTc interval prolongation is estimated to be higher in DCAN patients compared to patients without DCAN in some studies, for example in a study in Nigeria by Ogba J Ukpabi *et al.* in 2017, the prevalence of prolonged QTc in DCAN was 12% as compared to 1.6% in DM patients without DCAN and 0.6% in patients with neither DCAN nor DM. However, in this study, the prolongation was not associated with the severity of DCAN [18].

In another study done in India by Gaurav Agarwal in 2017, an increased prevalence of QTc prolongation in the DCAN group (56%) was associated with the severity of DCAN and cardiac arrhythmias [18].

3. Methodology

3.1. Study Area

The study was conducted at the medical outpatient clinic in Bugando Zonal Centre Referral Hospital, a tertiary consultant and teaching hospital located in Mwanza City with a 950-bed capacity. The city is located on the southern shores of Lake Victoria in the Northwest part of the United Republic of Tanzania. BMC is a referral center for seven neighboring regions namely Mara, Kagera, Shinyanga, Simiyu, Kigoma, Tabora, and Geita. The BMC DM outpatient care clinic attends about 70 - 90 DM patients per week.

3.2. Study Design

It was the hospital-based descriptive cross-sectional study that conducted at Bugando Zonal Referral Hospital, Mwanza Tanzania

3.3. Study Participants

All adult patients known to have DM, aged 18 years and above are registered and attend DM Clinic at BMC regardless of DM type, on medication/insulin, or not on medication during research activity.

3.4. Sampling and Sample Size

The sample was selected using a systematic random sampling technique to recruit participants who met the inclusion criteria.

The sample size was calculated using the Kish Leslie formula:

$$n = Z^2 PQ/D^2 ,$$

whereas:

n = estimated sample size

Z = level of confidence
P = Estimated prevalence of DCAN
$Q = 1 - P$
D = Level of precision

3.5. Data Collection

Data was collected using standardized Questionnaires and patients' hospital electronic files.

3.6. Study Variables

3.6.1. Dependent Variables

Diabetic cardiac autonomic neuropathy (DCAN) was the dependent variable.

3.6.2. Independent Variables

The independent variables were Age, Sex, Occupation, Race, Residency, alcohol, smoking history, Duration of the disease (DM, HTN), the medication used, BMI, Heart rate, BP, and HbA1c.

3.7. Inclusion Criteria

All adult DM patients diagnosed with DCAN aged 18 years and above are registered in the BMC Patients database regardless of the type of DM and whether they are on treatment or not.

3.8. Exclusion Criteria

DCAN patients with a documented history of Thyroid disease or other endocrinopathies, heart failure, and cardiac arrhythmias were excluded.

3.9. Data Management and Statistical Analysis

Data from the questionnaire was verified, entered in Microsoft Excel, and cleaned. STATA version 15 was used. This STATA 15 Version is manufactured by StataCorp LLC and is located at 4905 Lakeway Drive, College Station, TX 77845, USA. This Stata 15 Version has the following features: Powerful data management capabilities, including data import/export from various formats, management of large datasets with efficient data manipulation functions, and an extensive range of statistical tests, models, and procedures; It includes linear and nonlinear models, time-series analysis, survival analysis, and more, high-quality, customizable graphs for data visualization, it includes a wide array of graphical options and the ability to export graphs in various formats, scripting and automation capabilities through Stata's programming language, ability to extend Stata's functionalities with user-written commands and packages, intuitive graphical user interface with command-line input, support for both novice and advanced users through accessible menus and comprehensive documentation. It operates well with Windows (Windows 7, 8, 10, and later versions) and macOS (OS X 10.9 Mavericks and later versions). It performed data cleaning, checking

for inconsistency or missing values, transformation of variables, generating, recoding variables, duplicate entries, or any unusual values (outliers) identified and removed prior to analysis. Continuous variables were summarized appropriately using mean with standard deviation or median with the interquartile range depending on the distribution. The Shapiro-Wilk W test was used to check whether the continuous variables were normally distributed, and 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.

3.10. Ethical Statement

Confidentiality was maintained, and patient identities from their hospital e-files remained closed and respected. The permission to conduct research using hospital patients' files from hospital records was obtained through the Hospital Management Team. The Ethical Clearance was obtained from the BMC Ethical Committee before the study began.

4. Results

During the study, a total of 200 diabetic patients with DCAN at Bugando Medical Centre (BMC) in Mwanza Region were screened from the Hospital patients' files database. Among the screened patients, 188 were eligible and enrolled in the study, and 12 candidates did not meet the inclusion criteria.

4.1. Baseline Socio-Demographic

This study enrolled 188 DCAN patients. The median age was 57 [IQR 52 - 56] among the study patients, 37.3% (70) were males and 62.7% (118) were females. Other characteristics are described in **Table 1**.

4.2. 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 ≥ 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 the presence of hypertension for more than 10 years (OR 2.29; 95% CI 1.33 - 3.95; p-value 0.003). 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 BMI more than 30 (OR 1.41; 95% CI 1.17 - 1.69; p-value < 0.001) and the 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, elevated triglycerides, LDL and reduced HDL, hypertension and DM duration though significantly associated with DCAN, were not analyzed by multivariate analysis due to collinearity with BMI and the presence of resting tachycardia. Other findings are shown in Table 2.

Table 1. Baseline socio-demographic data of study participants at BMC (n = 383).

Characteristic	Numbers	Percentage (%)
Gender		
Males	70	37.3
Females	118	62.7
Age (years)		
18 - 39 years	10	10.7
40 - 59 years	100	53.3
≥ 60 years	68	36.0
Marital Status		
Single	1	0.5
Married	156	83
Divorced/separated/widowed	31	16.5
Level of education		
No formal education	13	6.8
Primary school education	115	61.1
Secondary education	33	17.8
Post-secondary and higher education	27	14.4
Source of income		
Farmer/peasant	106	56.4
Petty traders/manual workers	41	22.2
Professional/business	26	14.9
No formal employment	12	6.5

5. Discussion

This study was conducted to evaluate the DCAN-associated factors, patterns and percentages among DM patients diagnosed with DCAN in Bugando Medical Centre. Diabetic Cardiac. This study revealed a remarkable association between BMI, Resting Tachycardia, more than 10 years of Diabetic Miletus (DM), more than 10 years of Hypertension, age above 60 years and hyperlipidemia as shown in Table 2 analyzed above. This emphasizes the importance of further studying these preven-

tive measures or interventions to rescue DM patients from this life-threatening complication in the general population.

Table 2. Factors associated with DCAN (n = 383).

VARIABLE	DCAN (%)	UNIVARIATE		MULTIVARIATE	
		OR [95% CI]	p-value	OR [95% CI]	p-value
AGE					
18 - 39 years	13 (6.9)	Ref			
40 - 59 years	92 (48.9)	1.77 (0.86 - 3.61)	0.117		
≥ 60 years	83 (44.1)	3.27 (1.55 - 6.82)	**0.002**	-*	-*
MARITAL STATUS					
Single	1 (0.5)	Ref			
Married	155 (82.5)	0.95 (0.06 - 15.33)	0.972		
Divorced/separated/widowed	32 (17.0)	1.03 (0.06 - 17.23)	0.982		
EDUCATION LEVEL					
No formal education	11 (5.9)	Ref			
Primary school education	123 (65.4)	1.51 (0.67 - 3.43)	0.323		
Secondary education	29 (15.4)	1.01 (0.41 - 2.53)	0.976		
Post-secondary and higher education	25 (13.3)	1.14 (0.44 - 2.91)	0.790		
Source of income					
Farmer/peasant	109 (58)	Ref			
Manual workers	45 (24)	1.10 (0.67 - 1.83)	0.699		
Professional	24 (12.8)	0.71 (0.40 - 1.29)	0.263		
Non-formal employment	10 (5.3)	0.65 (0.28 - 1.52)	0.325		
DM duration					
0 - 4 years	44 (23.4)	Ref			
5 - 9 years	48 (25.5)	1.88 (1.10 - 3.21)	**0.021**	1.49 (0.83-2.69)	0.186
≥ 10 years	96 (51.1)	3.43 (2.10 - 5.59)	**< 0.001**	-*	-*
DM duration					
0 - 4 years	44 (23.4)	Ref			
5 - 9 years	48 (25.5)	1.88 (1.10 - 3.21)	**0.021**	1.49 (0.83-2.69)	0.186
≥ 10 years	96 (51.1)	3.43 (2.10 - 5.59)	**< 0.001**	-*	-*
BMI					
Normal weight (18.5 - 24.9)	49 (26.1)	Ref			
Overweight (25 - 29.9)	85 (45.2)	1.73 (1.09 - 2.76)	**0.020**	1.37 (0.83-2.27)	0.222
Obese (≥ 30)	54 (2)	3.15 (1.78 - 5.59)	**0.000**	2.27 (1.20-4.30)	**< 0.001**

Continued					
HbA1C (%)					
Controlled (≤ 7)	92 (49.0)	Ref			
Poorly controlled (> 7)	96 (51.0)	2.91 (1.58 - 3.66)	**0.000**	-*	-*
HDL (mmol/l)					
Normal (≥ 1)	60 (32.0)	Ref			
Abnormal (< 1)	128 (68.0)	4.27 (2.78 - 6.54)	**0.000**	-*	-*
LDL (mmol/l)					
Normal (≤ 3.4)	47 (25)	Ref			
Abnormal (> 3.4)	141 (75)	4.50 (2.91 - 6.97)	**0.000**	-*	-*
Triglycerides (mmol/l)					
Normal (≤ 1.7)	62 (33.0)	Ref			
Abnormal (> 1.7)	126 (67.0)	3.88 (2.54 - 5.93)	**0.000**	-*	-*

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

5.1. Factors Associated with Diabetic Cardiac Autonomic Neuropathy

This study has revealed a significant association between DCAN and BMI of more than 30. The majority of our DCAN population were either overweight or obese, 23% and 18% respectively. Overweight and obesity have been associated with increased insulin resistance contributing to the etiology of metabolic syndrome, progression, and development of DCAN. Multiple other studies, including have shown an association between a higher BMI and DCAN. [14] Findings from Muhanad M. Dhumad *et al.*, showed no association between DCAN and BMI 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 meta-analysis revealed that waist-hip ratio is a better predictor for cardiovascular risk occurrence than BMI. [15]

The DCAN shows significantly associated with Co-morbidities like the presence of hypertension for more than 10 years (OR 2.29; 95% CI 1.33 - 3.95; p-value 0.003). 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). In a meta-analysis by Dafaalla *et al.* in 2016, there was a significant association of DCAN with Hypertension, advanced age, long duration of DM, high serum triglycerides, and higher BMI among other risk factors that agreed with the results of this study. [16]

Additionally, the current study shows resting tachycardia has significantly been associated with DCAN. This is due to abnormalities in the parasympathetic and sympathetic function, resting tachycardia and postural hypotension have been some of the clinical manifestations of DCAN. [14]

5.2. Study Limitation

This was a cross-sectional study, thus, the causal effect relationship was not achieved, hence calling for more extensive cohort studies to establish the causal effect relationship.

1) The study did not represent the general population since it was a single-centered hospital-based study.

2) Typic error of entrance errors during patient registration in hospital files can cause some slight deviation in the outcome.

3) Only limited factors were taken into consideration, some other clinical, imaging, and lab factors can be traced in their association with DCAN.

6. Conclusion

DCAN is prevalent among DM patients attending medical outpatient clinics at BMC. BMI, Resting Tachycardia, more than 10 years of Diabetic Miletus (DM), more than 10 years of Hypertension, age above 60 years, and hyperlipidemia, poorly controlled DM with HbA1C more than 7% were statistically found to be significantly associated with DCAN development among DM patients. Immediately, measures should be taken to address these associated factors, and most of them can be prevented and controlled with clinical or public health interventions to rescue DM patients against this life-threatening complication (DCAN) in communities at large.

6.1. Recommendation

1) Modifiable associated factors should be assessed, and patient care improved to prevent the development and progression of DCAN.

2) Clinical and Public health communities should combine and strongly address these associated factors to reduce mortality and improve the quality of life among DM patients.

3) Public Health communities may use the results of this study to develop proper interventions to reduce or prevent the development of DCAN among DM population.

4) This study calls for bigger cohort and population-based studies, to establish a causal effect relationship as well as a follow-up for the current patients diagnosed with DCAN.

6.2. Dissemination of Results

Results from this study will be published in peer-reviewed journals for reference.

Acknowledgments

Sincere gratitude to the study participants, Bugando Medical Centre management, Dr. Tariq, my colleagues Dr. Sabrina Kumlin, Dr. Isaack Ajee, Dr. Bantar Tawe, and my family for their endless support from the beginning to the end of this dissertation. Finally, special thanks to data clerks at BMC for their great

support during data collection.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Lin, X., Xu, Y., Pan, X., Xu, J., Ding, Y., Sun, X., *et al.* (2020) Global, Regional, and National Burden and Trend of Diabetes in 195 Countries and Territories: An Analysis from 1990 to 2025. *Scientific Reports*, **10**, Article No. 14790. https://doi.org/10.1038/s41598-020-71908-9

[2] Migisha, R., Agaba, D.C., Katamba, G., Kwaga, T., Tumwesigye, R., Miranda, S.L., *et al.* (2020) Prevalence and Correlates of Cardiovascular Autonomic Neuropathy among Patients with Diabetes in Uganda: A Hospital-Based Cross-Sectional Study. *Global Heart*, **15**, Article 21. https://doi.org/10.5334/gh.765

[3] Elegbede, O.E., Sanni, T.A. and Alabi, A.K. (2022) Prevalence and Risk Factors Associated with Diabetes Mellitus in Public Secondary Schools Teachers in Ekiti State. *Ibom Medical Journal*, **15**, 95-101. https://doi.org/10.61386/imj.v15i2.246

[4] Andersen, S.T., Witte, D.R., Fleischer, J., Andersen, H., Lauritzen, T., Jørgensen, M.E., *et al.* (2018) Risk Factors for the Presence and Progression of Cardiovascular Autonomic Neuropathy in Type 2 Diabetes: Addition-Denmark. *Diabetes Care*, **41**, 2586-2594. https://doi.org/10.2337/dc18-1411

[5] Omar, M., Wieben, E.S., Polcwiartek, C., Fleischer, J., Valentin, J.B., Aagaard, J., *et al.* (2021) Cardiovascular Autonomic Neuropathy in Patients with Schizophrenia. *Nordic Journal of Psychiatry*, **75**, 547-552. https://doi.org/10.1080/08039488.2021.1902566

[6] Khatoon, N., Santhosh Kumar, B. and Hannan Hazari, M.A. (2010) Cardiovascular Autonomic Neuropathy in Patients with Diabetes Mellitus. *International Journal of Pharma and Bio Sciences*, **1**, 17-39.

[7] Dafaalla, M.D., Nimir, M.N., Mohammed, M.I., Ali, O.A. and Hussein, A. (2016) Risk Factors of Diabetic Cardiac Autonomic Neuropathy in Patients with Type 1 Diabetes Mellitus: A Meta-Analysis. *Open Heart*, **3**, e000336. https://doi.org/10.1136/openhrt-2015-000336

[8] Amour, A.A., Chamba, N., Kayandabila, J., Lyaruu, I.A., Marieke, D., Shao, E.R. and Howlett, W. (2019) Prevalence, Patterns, and Factors Associated with Peripheral Neuropathies among Diabetic Patients at Tertiary Hospital in the Kilimanjaro Region: Descriptive Cross-Sectional Study from North-Eastern Tanzania. *International Journal of Endocrinology*, **2019**, Article 5404781. https://pubmed.ncbi.nlm.nih.gov/31275374/ https://doi.org/10.1155/2019/5404781

[9] Blok-Husum, L., Brcelic, M.A.R., Bassi, H.K.F.K., Jensen, S.E., Nielsen, R.E., Kragholm, K., *et al.* (2023) Cardiovascular Autonomic Reflex Tests Using a Handheld Device in the Diagnosis of Cardiovascular Autonomic Neuropathy in Patients with Schizophrenia. *American Heart Journal Plus: Cardiology Research and Practice*, **26**, Article 100252. https://doi.org/10.1016/j.ahjo.2023.100252

[10] Eleftheriadou, A., Williams, S., Nevitt, S., Brown, E., Roylance, R., Wilding, J.P.H., *et al.* (2020) The Prevalence of Cardiac Autonomic Neuropathy in Prediabetes: A Systematic Review. *Diabetologia*, **64**, 288-303. https://doi.org/10.1007/s00125-020-05316-z

[11] Migisha, R., Agaba, D.C., Katamba, G., Kwaga, T., Tumwesigye, R., Miranda, S.L., *et al.* (2020) Prevalence and Correlates of Cardiovascular Autonomic Neuropathy among Patients with Diabetes in Uganda: A Hospital-Based Cross-Sectional Study. *Global Heart*, **15**, Article 21. https://doi.org/10.5334/gh.765

[12] Dimitropoulos, G. (2014) Cardiac Autonomic Neuropathy in Patients with Diabetes Mellitus. *World Journal of Diabetes*, **5**, 17-39. https://doi.org/10.4239/wjd.v5.i1.17

[13] Andersen, S.T., Witte, D.R., Andersen, H., Bjerg, L., Bruun, N.H., Jørgensen, M.E., *et al.* (2018) Risk-Factor Trajectories Preceding Diabetic Polyneuropathy: Addition-Denmark. *Diabetes Care*, **41**, 1955-1962. https://doi.org/10.2337/dc18-0392

[14] Schönauer, M., Thomas, A., Morbach, S., Niebauer, J., Schönauer, U. and Thiele, H. (2008) Cardiac Autonomic Diabetic Neuropathy. *Diabetes and Vascular Disease Research*, **5**, 336-344. https://doi.org/10.3132/dvdr.2008.047

[15] Rukadikar, C., Rukadikar, A. and Kishore, S. (2023) A Review on Autonomic Functional Assessment in Diabetic Patients. *Cureus*, **15**, e34598. https://doi.org/10.7759/cureus.34598

[16] Bissinger, A. (2017) Cardiac Autonomic Neuropathy: Why Should Cardiologists Care about That? *Journal of Diabetes Research*, **2017**, Article 5374176. https://doi.org/10.1155/2017/5374176

[17] Ukpabi, O.J. and Onwubere, B.J. (2018) QTc Prolongation in Black Diabetic Subjects with Cardiac Autonomic Neuropathy. *African Health Sciences*, **17**, 1092-1100. https://doi.org/10.4314/ahs.v17i4.17

[18] Tripathy, J.P., Thakur, J.S., Jeet, G., Chawla, S., Jain, S., Pal, A., *et al.* (2017) Prevalence and Risk Factors of Diabetes in a Large Community-Based Study in North India: Results from a STEPS Survey in Punjab, India. *Diabetology & Metabolic Syndrome*, **9**, Article No. 8. https://doi.org/10.1186/s13098-017-0207-3

Abbreviation

BMC	Bugando Medical Centre
BMI	Body Mass Index
DCAN	Diabetic Cardiac Autonomic Neuropathy
DM	Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
T1DM	Type 1 Diabètes Mellitus
JLI	James Lind Institute
HDL	High Density Lipoprotein
LDL	Low Density Lipoprotein
TG	Triglycerides
HR	Heart Rate
HTN	Hypertension
MOPD	Medical Outpatient Department
DBP	Diastolic Blood Pressure
SBP	Systolic Blood Pressure
PR	Pulse Rate