

ORIGINAL RESEARCH

Prevalence and Correlates of Cardiovascular Autonomic Neuropathy Among Patients with Diabetes in Uganda: A Hospital-Based Cross-sectional Study

Richard Migisha¹, David Collins Agaba¹, Godfrey Katamba², Teddy Kwaga³, Raymond Tumwesigye⁴, Silvia Lopez Miranda¹, Anthony Muyingo⁵ and Mark J. Siedner^{5,6}

¹ Department of Physiology, Mbarara University of Science and Technology, Mbarara, UG

² Department of Physiology, St. Augustine International University, Kampala, UG

³ Department of Ophthalmology, Mbarara University of Science and Technology, Mbarara, UG

⁴ Department of Nursing, Mbarara University of Science and Technology, Mbarara, UG

⁵ Department of Internal Medicine, Mbarara University of Science and Technology, Mbarara, UG

⁶ Department of Medicine, Massachusetts General Hospital, Boston, US

Corresponding author: Richard Migisha (migisha85@gmail.com)

Background: Cardiovascular autonomic neuropathy (CAN) is a common complication in individuals with diabetes mellitus (DM) but often overlooked in clinical practice. The burden and correlates of CAN have not been extensively studied in low-income countries, particularly in sub-Saharan Africa.

Objectives: To determine the prevalence and correlates of CAN among adults in ambulatory diabetes care in southwestern Uganda.

Method: We conducted a cross-sectional study among adults with diabetes from November 2018 to April 2019. CAN was assessed using the five autonomic function tests: deep breathing, Valsalva maneuver, postural index on standing, change in blood pressure during standing and diastolic blood pressure response to isometric exercise. We estimated the prevalence of CAN and fit regression models to identify its demographic and clinical correlates.

Results: We enrolled 299 individuals. The mean age was 50.1 years (SD \pm 9.8), mean HbA1c was 9.7 (SD \pm 2.6) and 69.6% were female. CAN was detected in 156/299 (52.2%) of the participants on the basis of one or more abnormal cardiovascular autonomic reflex tests. Out of 299 participants, 88 (29.4%) were classified as early CAN while 61/299 (20.4%) and 7/299 (2.3%) were classified as definite and severe (advanced) CAN respectively. In multivariable regression models, age over 50 years (aOR 3.48, 95%CI 1.35 –8.99, $p = 0.010$), duration of diabetes over 10 years (aOR 4.09, 95%CI 1.78 –9.38, $p = 0.001$), and presence of diabetic retinopathy (aOR 2.25, 95%CI 1.16 –4.34, $p = 0.016$) were correlated with CAN.

Conclusions: Our findings reveal a high prevalence of CAN among individuals in routine outpatient care for diabetes mellitus in Uganda. Older age, longer duration of diabetes and coexistence of retinopathy are associated with CAN. Future work should explore the clinical significance and long term outcomes associated with CAN in this region.

Keywords: Cardiovascular autonomic neuropathy; Prevalence; Diabetes; Uganda

Background

The global prevalence of diabetes is 8.5%, with an estimated 422 million people living with the disease [1]. As of 2014, the prevalence of diabetes was higher in low-income (7.4%) than in high-income (7.0%) countries [2]. Moreover, it is estimated that the disease burden will increase by approximately 70% in low income countries by 2030 [3, 4]. Sub-Saharan Africa, in particular, is believed to have the highest proportion of undiagnosed diabetes with more than two-thirds of people with diabetes unaware of their status [5, 6].

Cardiovascular autonomic neuropathy (CAN) is defined as an impairment of cardiovascular autonomic control in people with diabetes with other causes excluded [7, 8]. Cardiovascular reflex tests that are based on provocative physiological maneuvers of the autonomic nervous system (Valsalva maneuver, supine to standing, deep breathing and sustained hand grip) are commonly used in the detection of CAN [9]. There is no particular algorithm for the diagnosis of CAN, though it is recommended that more than one test be carried out to increase the reliability and sensitivity for proper diagnosis of the condition [10]. The occurrence of CAN, on the basis of at two or more tests [7, 11, 12] ranges from approximately 20% to 65%, with older age and longer duration of disease [13, 14]. CAN is associated with an increased risk of cardiac arrhythmias, silent myocardial ischemia and sudden death [10, 15]. Hence, it may limit exercise capacity and is associated with an increased risk of adverse cardiovascular events during exercise [16]. Moreover CAN is associated with increased risk of mortality [17]. Previous longitudinal studies among diabetic individuals with CAN have reported five-year mortality rates of up to 50%, often due to sudden cardiac death [18]. Despite these complications, CAN remains largely undiagnosed among individuals with diabetes. Nonetheless, early detection and treatment of CAN may prevent cardiovascular complications in diabetic patients [19], since there is evidence to suggest that cardiovascular denervation can be reversed early in the course of the condition [9, 20].

Despite the high prevalence of diabetes in low-resource settings, most studies on prevalence and correlates of CAN have been done in high-resource settings. There are particularly few data on the condition in Sub-Saharan Africa. In this clinic-based survey, we aimed to determine the prevalence and correlates of CAN among individuals with diabetes in ambulatory diabetes care in southwestern Uganda.

Methods

Study population

This cross-sectional study was conducted at the diabetes and endocrinology outpatient clinic of Mbarara Regional Referral Hospital (MRRH), Western Uganda. MRRH is a government-operated referral centre and the teaching hospital of the Medical School of Mbarara University of Science and Technology (MUST), serving a population of over four million people in its catchment area. The diabetes and endocrinology ambulatory care clinic is operated once per week and attends to an average of 100 patients per week. A total of about 1,500 diabetic patients are registered at the clinic.

Study participants were individuals with diabetes attending MRRH diabetes and endocrinology ambulatory clinic. We included participants aged 18 to 65 years with a clinical diagnosis of diabetes. We defined diabetes in those with a fasting blood glucose concentration greater than 7.0 mmol/l, or in those actively taking medications for diabetes [21–23]. We excluded individuals with a self-reported history of cardiac, respiratory, renal, hepatic, cerebrovascular, thyroid or other endocrine abnormalities. We also excluded individuals with previous ECG abnormalities, an acute illness in the last 48 hours, and those who had consumed beverages containing caffeine or alcohol within the past 12 hours. Finally, we excluded individuals actively taking calcium channel blockers or beta-blockers, which can interfere with the CAN screening battery [24].

Study Procedures and Definitions

We administered a standardized questionnaire to capture data on socio-demographic and clinical characteristics, including their data on smoking, alcohol use and diabetes treatment history. The diabetes treatment history was self-reported and verified by clinic records for those participants who had a chart available for review. Height, weight, hip circumference, and waist circumference were collected. We computed body mass index (BMI) by dividing participants' weight (in kilograms) by the height in metres squared (m^2), and categorized BMI as normal, underweight, overweight and obese [25]. Abdominal obesity was defined as a waist circumference ≥ 102 cm in males and ≥ 88 cm in females [25]. Blood pressure was measured using an upper arm automated sphygmomanometer (Omron HEM 705 LP, Omron Healthcare, Inc., Bannockburn, IL, USA) in a seated position. Participants were considered to have arterial hypertension if their blood pressure values were $\geq 140/90$ mmHg and/or taking medications for hypertension [26]. Intensity of physical activity was expressed in metabolic equivalent task (MET) as derived from the questionnaire using the WHO GPAQ analysis tool [27]. The presence of diabetic retinopathy was detected with direct ophthalmoscopy after pupillary dilation by an ophthalmologist. Diabetic retinopathy was classified or graded as non-proliferative (NPDR) and proliferative diabetic retinopathy (PDR). We assessed for the presence of the following symptoms of distal peripheral neuropathy over the preceding 6 months: numbness or 'dead feeling' in the feet; a tingling sensation in the feet; deep, painful or burning aches in the lower limbs; and unusual failure in walking uphill or climbing staircases. The existence of one or more of the symptoms was classified as abnormal. Hemoglobin A1c (HbA1c) was measured according to the standard operating procedure of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) [28] using an automated high performance

liquid chromatography analyzer (Cobas Integra 400, Roche diagnostics, Basel, Switzerland) at the Lancet Laboratories.

The evaluation of CAN was done according to standardized protocols described previously [12]. Briefly, we considered five measures to diagnosis CAN, including: 1) deep breathing; 2) Valsalva maneuver; 3) postural index on standing; 4) change in blood pressure during standing and 5) diastolic blood pressure response to isometric exercise. A resting 12-Lead electrocardiogram (ECG) was taken for all the participants using a portable ECG machine (Edan Instruments, Inc., Hessen, Germany).

Deep breathing

While lying down, participants were asked to perform a deep and slow inspiration up to the maximum total lung capacity for five seconds, which was followed by a forced expiration down to the residual volume for five seconds. The time to alternate the respiratory cycle was signaled directly to the patient by the attending research assistant. We calculated the maximum and minimum R-R interval during the respiratory cycle, and converted these results to beats per minute. We defined R-R interval as the duration between two successive R waves. We considered a variation of less than 15 beats per minute between the two measures as abnormal.

Valsalva maneuver

We asked participants to exhale into a mouthpiece with their nose closed and to perform a continuous expiratory effort. This was equivalent to an intraoral pressure of 40 mmHg, for 15 seconds. We then asked participants to release the strain, and to breathe regularly until the end of the test. We calculated the ratio of the longest RR interval to the shortest RR interval following the pressure release. We considered a ratio less than 1.2 as abnormal. The test was performed three times, and we used the mean value in our analyses. Participants with evidence of proliferative retinopathy were excluded from the valsalva maneuver, because it is associated with a minor risk of intraocular hemorrhage or lens dislocation [7].

Measurement of postural index on standing

We again asked participants to lie supine quietly. After about 5 minutes with continuous monitoring, the participant was made to stand. We calculated the postural index (PI) by measuring the heart rate response to the change of position from recumbent to standing over 180 seconds after getting up. We calculated this as the '30–15 ratio,' defined as the longest RR interval of beats 20–40 divided by the shortest RR interval of beats 5–25, starting from the first beat during the process of standing up. The postural index of <1.00 was considered abnormal.

Change in blood pressure during standing

We measured blood pressure with participants in recumbent position, every minute for three minutes, and then while standing, every minute for five minutes. We considered a drop of ≥ 20 mmHg in systolic blood pressure or ≥ 10 mmHg in diastolic blood pressure as abnormal.

Diastolic blood pressure response to isometric exercise

We asked participants to squeeze a hydraulic hand dynamometer (Lafayette Instrument Company, Lafayette, IN, USA) at 1/3 of the maximum effort for about 5 minutes. We considered an abnormal diastolic blood pressure in response to isometric exercise as an increase in diastolic blood pressure <15 mmHg.

Measurement of QT interval

We measured the QT interval from the beginning of the QRS complex to the end of the down-slope of the T wave (crossing of the isoelectric line); when a U wave was present, the QT interval was measured until the bottom of the angle between the T and U waves [29]. We used Bazette's formula to calculate a heart rate-corrected QT (QTc) [30]. QTc was the mean of QTc from five consecutive cycles in lead V5. We consider a maximum value of the QTc interval >440 ms to be elevated [31]. For quality control, two independent observers (DCA and GK) measured intervals. Both were blinded to participants' data, and an average measure taken. The Pearson's correlation coefficients for the agreement between the two observers were 0.92 and 0.87 for QTc and RR Intervals respectively. We performed ECG on the same day as glycaemic testing.

Sample size

A sample size of 296 participants was required to enable a 5% precision with a 95% confidence interval around an estimated CAN prevalence of 20% [32]. We entered data into EpiData3. (EpiData, Odense, Denmark), and used Stata for all analyses (StataCorp, College Station, Texas, USA).

Statistical Analyses

Our outcome of interest was CAN, defined by the results of each of the above five classification components. We categorized CAN based on severity, as described previously (**Table 1** [33]). We summed the points from each test to arrive at an overall CAN score, categorized as absent (0 points), early (0.5–1.5 points), definite (2–3 points), and severe (≥ 3.5 points) [12, 34].

We first described the participant characteristics. Next we estimated the prevalence of CAN as the proportion of patients meeting the definition of CAN. We then assessed for differences in demographic and clinical characteristics comparing those with and without CAN, using chi-square testing to compare categorical variables, student t-tests for continuous variables, and Wilcoxon rank-sum test for non-normally distributed continuous variables. Finally, we fit logistic regression models to identify correlates of CAN. Covariates with a *P*-value ≤ 0.2 in univariable models were included in multivariable models through backward stepwise elimination method. QTc interval was deliberately not included in the final model because it predicted the outcome perfectly.

Results

Out of the 512 diabetic patients screened for inclusion into the study between November 2018 and April 2019, we present results for 299 participants. The reasons for exclusion are described in **Figure 1**.

Demographic and clinical characteristics

Social and demographic characteristics of study participants with and without CAN are presented in **Table 2**. Most participants were female (69.6%) and peasants by occupation (58.6%). More than half (69.9%) of the participants had never taken alcohol. The mean age of the participants was 50.1 (SD \pm 9.8) years. Sev-

Table 1: Algorithm for classification of CAN (CAN score).

Tests	Point 0	Point 0.5	Point 1
Resting heart rate	<100 beats/min	100–110 beats/min	>110 beats/min
Postural hypotension (fall in systolic blood pressure)	<20 mmHg	20–30 mmHg	>30 mmHg
Valsalva ratio	>1.2	1.2–1.10	<1.10
Heart rate variability on deep breathing	>15 beats/min	15–10 beats/min	<10 beats/min
Increase in diastolic blood pressure during sustained handgrip	>15 mmHg	15–10 mmHg	<10 mmHg

CAN: Cardiovascular autonomic neuropathy.

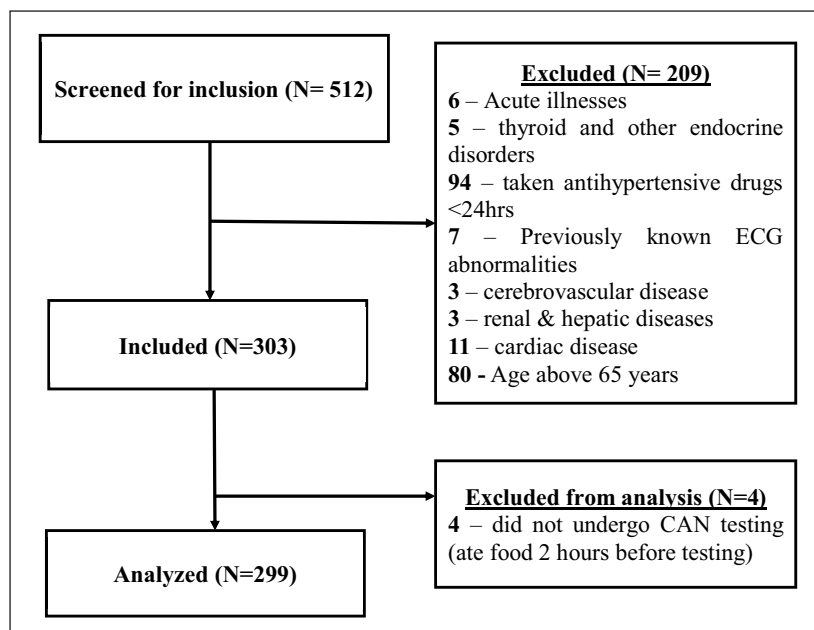


Figure 1: Study profile.

Table 2: Baseline demographic and clinical characteristics by CAN status.

Characteristic	Total cohort (N = 299)	Positive for CAN (N = 156)	No evidence of CAN (N = 143)	P value
Age, in years, mean (SD)	50.1 (±9.8)	52.8 (±8.7)	47.2 (±10.2)	<0.001
Female sex (%)	208 (69.6)	122 (78.2)	86 (60.1)	0.001
Ever attended school, yes (%)	233 (77.9)	115 (73.7)	118 (82.5)	0.067
Occupation				
Peasant (%)	175 (58.5)	103 (66.0)	72 (50.4)	0.006
Student (%)	6 (2.0)	2 (1.3)	4 (2.8)	0.351
Businessman (woman) (%)	64 (21.4)	29 (18.6)	35 (24.5)	0.215
Civil servant (%)	51 (17.1)	26 (16.7)	25 (17.5)	0.851
Ever smoked, yes (%)	70 (23.4)	37 (23.7)	32 (22.4)	0.783
Currently smoking, yes (%)	18 (25.7)	11 (29.0)	7 (21.9)	0.500
Duration of diabetes in years, mean (SD)	5.8 (±5.9)	7.5 (±6.9)	3.9 (±3.9)	<0.001
BMI (kg/m²), mean (SD)	27.4 (±5.6)	27.5 (±5.9)	27.3 (±5.2)	0.685
Waist circumference in cm, mean (SD)	98.2 (±13.6)	99.9 (±14.3)	96.4 (±12.7)	0.025
History of vigorous physical activity (≥600 METS/Week) (%)	173 (57.9)	89 (57.1)	84 (58.7)	0.087
Fasting blood sugar in mmol/L, mean (SD)	11.2 (±4.8)	11.8 (±5.2)	10.5 (±4.3)	0.021
HbA1c (%), mean(SD)	9.7 (±6.7)	9.7 (±2.5)	9.6 (± 2.7)	0.506
Resting heart rate in beats/min, mean (SD)	76.6 (±13.1)	79.2 (±14.7)	73.6 (±10.4)	<0.001
Systolic blood pressure in mmHg, mean (SD)	141.7 (±22.6)	148.6 (±23.2)	134.2 (±19.4)	<0.001
Diastolic blood pressure in mmHg, mean (SD)	87.1 (±10.7)	88.8 (±10.7)	85.4 (±10.5)	0.006
Pulse pressure in mmHg, mean (SD)	54.6 (±17.8)	59.9 (±19.4)	48.8 (±13.8)	<0.001
Mean arterial pressure (mmHg)	105.3 (±13.3)	108.7 (±13.1)	101.6 (±12.5)	<0.001
Retinopathy				<0.001
None (%)	231 (77.3)	106 (68.0)	125 (87.4)	
Non-proliferative (%)	53 (17.7)	35 (22.4)	18 (12.6)	
Proliferative (%)	15 (5.0)	15 (9.6)	0 (0.0)	
History of neuropathy symptoms in past 6 months				
Palpitations, yes (%)	149 (49.8)	93 (59.6)	56 (39.2)	<0.001
Fainting or blackouts, yes (%)	114 (38.1)	63 (40.4)	51 (35.7)	0.401
'Dead feeling', pricking or burning sensation in the feet, yes (%)	183 (61.2)	105 (67.3)	78 (54.6)	0.024
QTc interval (ms), mean (SD)	428.4 (±22.3)	438.4 (±22.0)	417.5 (±16.8)	<0.001

SD: Standard deviation; CAN: Cardiovascular Autonomic Neuropathy; MET: Metabolic Equivalent Task.

enty participants (23.4%) had ever smoked. The clinical characteristics of the participants with and without CAN are presented in **Table 2**. The mean duration of diabetes was four years (IQR 1, 8). The mean fasting blood glucose and HbA1c were 11.2 mmol/l (SD ± 4.8) and 9.7% (SD ± 2.6), respectively. Out of the 299 participants, 68 (22.7%) had diabetic retinopathy.

Prevalence and correlates of CAN

CAN was diagnosed in 156/299 participants for a prevalence of 52.2% (95% CI 46.3–58.0%) on the basis of one or more abnormal cardiovascular autonomic reflex tests. The classification of CAN on the basis of CAN score is presented in **Table 4**. Out of 299 participants, 88 (29.4%) were classified as early CAN while 61/299

(20.4%) and 7/299 (2.3%) were classified as definite and severe (advanced) CAN respectively on the basis of the CAN score. The prevalence of CAN as assessed by the various measures of autonomic neuropathy is presented in **Table 3**. The most common positive sub-scale of CAN was abnormal heart rate variability with deep breathing, which we detected in 125 individuals (42%). The prevalence and severity of CAN was highest in older age groups as shown in **Figure 2**.

Participants with CAN had a significantly longer duration of diabetes ($p < 0.001$), higher waist circumference ($p = 0.025$), higher systolic blood pressure ($p < 0.001$), higher diastolic blood pressure ($p = 0.001$) and higher resting pulse rate ($p < 0.001$) compared to those without CAN. The proportion of patients with history of palpitations ($p < 0.001$) and numbness in feet ($p = 0.024$) was significantly more among participants with CAN compared to others. The mean pulse pressure, mean arterial pressure and QTc interval were significantly higher in participants with CAN compared to those without CAN ($p < 0.001$).

In multivariable regression models, significant correlates of CAN were: age over 50 years (aOR 3.48, 95%CI 1.35–8.99, $p = 0.010$), duration of diabetes over 10 years (aOR 4.09, 95%CI 1.78–9.38, $p = 0.001$) and presence of diabetic retinopathy (aOR 2.25, 95%CI 1.16–4.34, $p = 0.016$), as shown in **Table 5**.

Discussion

In the study of ambulatory diabetic patients in Uganda, we identified a prevalence of CAN of 52.2% (95% CI 46.3–58.0%), on the basis of at least one or more abnormal cardiovascular autonomic reflex tests. In adjusted regression models, CAN was more common in those over 50, people with diabetes for over 10 years and those with diabetic retinopathy. Our results, which as far as we know are the first from the region, demonstrate a remarkably high rate of autonomic neuropathy in the East African region, and motivate an important need to better explore this preventable and morbid condition in this population.

The prevalence of CAN (52.2%) in our study is comparable with findings from several studies elsewhere in lower and middle-income countries (LMICs) that have reported values between 45% and 60% [35–39]. Much lower prevalence estimates of CAN were reported elsewhere, particularly in higher-income countries. For instance, prevalence estimates between 15–34% have more recently been reported in Germany, Canada, United States and England [40–43]. We suspect that the high prevalence of CAN reported in our study and

Table 3: Prevalence of CAN by the different assessment methods.

Test/Method	Number of cases (n)	percentage, n/N (%)
N = 299		
Resting tachycardia (pulse rate ≥ 100 bpm)	17	5.7
Abnormal postural index (≤ 1.0)	40	13.4
HRV: Reduced E/I ratio with deep breathing (< 15 bpm),	125	41.8
Valsalva ratio: (< 1.2), (N = 284)*	52	18.3
Postural hypotension	52	17.4
Diastolic BP response to sustained hand grip (< 15 mmHg)	108	36.1

HRV: Heart rate variability; E/I: Expiration to inspiration ratio.

* Sample size is less by 15 participants who had proliferative retinopathy and were excluded from the valsalva maneuver.

Table 4: Prevalence of CAN by severity (Classification of CAN).

CAN category	Number of cases (n)	Percentage, n/N (%)
N = 299		
Absent	143	47.8
Early	88	29.4
Definite/Confirmed	61	20.4
Severe/Advanced	7	2.3
TOTAL	299	100.0

Table 5: Demographic and clinical factors correlated with CAN.

Characteristic	% CAN positive	Univariable Analysis		Multivariable Analysis	p value
	n/N (%)	OR 95%CI	p value	aOR 95%CI	
Age category(years)					
<35	7/29 (24.1)		Ref		Ref
35–50	39/86 (45.4)		2.61 (1.01–6.75)	0.048	2.10 (0.77-5.74)
51–65	110/184 (59.8)		4.67 (1.90–11.49)	0.001	3.48 (1.35–8.99)
Sex					
Male	34/91 (37.4)		Ref		Ref
Female	122/208 (58.7)		2.38 (1.43–3.95)	0.001	1.85 (0.94-3.66)
Duration of diabetes in years					
<5years	74/170 (43.5)		Ref		Ref
5–9 years	38/76 (50.0)		1.30 (0.75–2.23)	0.347	1.04 (0.58–1.88)
10 years and above	44/53 (83.0)		6.34 (2.91–13.81)	<0.001	4.09 (1.78–9.38)
Fasting blood sugar category					
≤7.0 mmol/L	24/60 (40.0)		Ref		Ref
>7.0 mmol/L	132/239 (55.2)		1.85 (1.04–3.29)	0.036	1.62 (0.86–3.04)
Blood pressure category					
≤130/80 mmHg	18/60 (30.0)		Ref		Ref
>130/80 mmHg	105/168 (62.5)		3.89 (2.06–7.33)	<0.001	
Waist circumference					
Normal fat distribution	26/62 (41.9)		Ref		Ref
Moderate central fat distribution	19/48 (39.6)		0.91 (0.42–1.95)	0.804	0.66 (0.28–1.55)
High central fat accumulation	111/189 (58.7)		1.97 (1.10–3.53)	0.022	1.16 (0.53–2.52)
Retinopathy					
Absent	106/231 (45.9)		Ref		Ref
Present	50/68 (73.5)		3.28 (1.80–5.95)	<0.001	2.25 (1.16–4.34)
History of Palpitations in past 6 months					
No	63/150 (42.0)		Ref		Ref
Yes	93/149 (62.4)		2.29 (1.44–3.65)	<0.001	
Symptoms of distal peripheral neuropathy					
No	51/116 (44.0)		Ref		Ref
Yes	105/183 (57.4)		1.72 (1.07–2.74)	0.024	
Resting heart rate					
≤85 beats/min	102/227(44.9)		Ref		Ref
>85 beats/min	54/72 (75.0)		3.68 (2.03–6.66)	<0.001	
QTc interval					
≤440 ms	74/213 (34.7)		Ref		Ref
>440 ms	82/86 (95.4)		38.51 (13.58–109.21)	<0.001	

aOR: Adjusted Odds Ratio; Ref: Reference Category; CI: Confidence interval; QTc: Heart rate corrected QT.

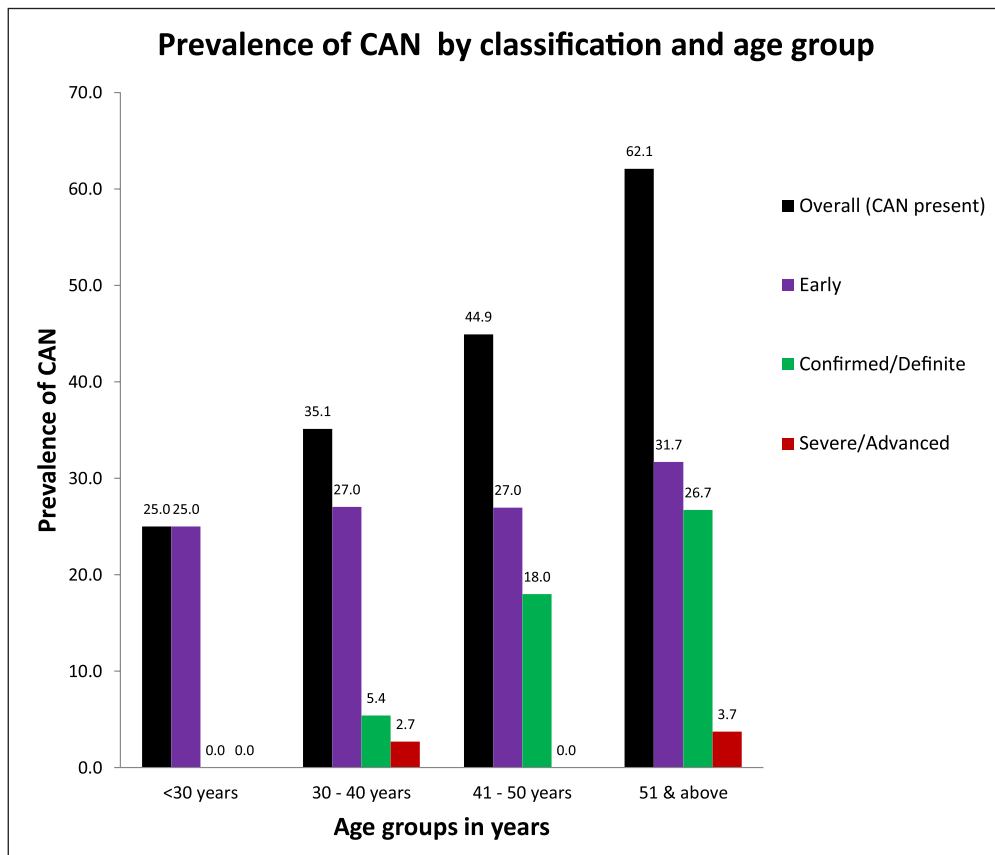


Figure 2: Graph showing variation of prevalence of CAN by severity with age.

others in LMICs is likely attributable to later diagnosis and poorer glycemic control in these study populations. The mean HbA1c for the study participants in the present study was 9.7% which was above the recommended target of <7.5% [44]. The variation in the prevalence also might be attributed to the different methodologies employed in the diagnosis and classification of CAN. In this study, we used cardiovascular autonomic reflex tests which are extensively used in research, and have become a reference standard for measurement of autonomic function [45], with high reported validity [46].

Both the duration of diabetes and diabetic complications such as retinopathy have also been reported as major correlates for CAN in several prior studies [7, 13, 15, 47–53]. This is believed to be due to the central role of chronic hyperglycemia in the pathogenesis of CAN and other micro-vascular complications. Although the mechanisms by which hyperglycemia predisposes to CAN are not completely understood [54], increased oxidative stress, accumulation of advanced glycosylated end products, accumulation of sorbitol, disruption of hexosamine and protein C kinase pathways are the metabolic factors implicated [46, 55, 56]. In contrast, we did not note a correlation between glycemic control and the presence of CAN in our study. We believe this is due to the lack of a sufficient proportion of participants with adequate glycemic control in this study. However, this could also be due to reverse causality where patients become more proactive in controlling their blood sugars after developing CAN and other diabetes-related complications. This can only be detected through longitudinal studies. Moreover, because of variability in glucose control, a single point estimate of HbA1c may not correlate with the degree of autonomic neuropathy [53]. However, longitudinal studies have shown that mean HbA1c correlates with future risk of diabetic autonomic neuropathy [50, 57]. Therefore, our study builds on the increasing body of evidence suggesting that other means of determining the severity of diabetes, such as the Homeostasis Model Assessment (HOMA), may be superior predictors of autonomic neuropathy [36, 58].

Finally, older age is also a recognized risk factor for CAN [37, 49, 59]. Several changes can occur in autonomic nervous system with advanced age [60]. These changes include: selective activation of the sympathetic nervous system [61] with concomitant increase in basal plasma noradrenaline concentrations [62] and altered adrenoceptor function with reduced sensitivity to adrenergic antagonists and agonists [63]. Thus, it is well established that the autonomic nervous system function deteriorates with aging [64]. Our study hence underscores the need for targeted screening of elderly diabetic patients for CAN, so as to modulate

diabetes therapeutic targets aimed at delaying the development and/or progression of CAN. The correlation with QTc interval prolongation demonstrated in our study, substantiates the recognized increased risk of adverse cardiovascular events such as cardiac arrhythmias and sudden death in patients with diabetic CAN [48, 65, 66].

Overall, our findings have important clinical and public health implications. We observed that most participants with diabetic CAN (88/156: 56%) had early CAN. There is emerging epidemiological evidence suggesting that there is a possibility of reversal of cardiovascular denervation in the early stages of the disease [9, 67]. Therefore, improving glycemic control, life style modifications and cardiovascular disease risk factors management could slow the progression of CAN or even reverse it in this population. The high burden of CAN detected in this study also confirms the importance for early and systematic screening for this complication among patients with diabetes.

Study Limitations

This study has some notable limitations. The study was conducted in one hospital and findings from the study may not be generalizable beyond the population of individuals in outpatient diabetes care in peri-urban Uganda. Additionally, the study was done in a regional referral hospital, and thus a referral bias may overestimate the prevalence seen in the community-based setting. That said, we excluded individuals with multi-morbidity, including known cardiovascular disease, and those >65 years old, to investigate the epidemiology of CAN in otherwise healthy individuals with diabetes. Many of our measures, including clinical history, alcohol and smoking use are self-reported, and susceptible to recall bias and social desirability bias. Another important limitation is the cross-sectional nature of the study, limiting our ability to assign the time directionality of association between CAN risk correlates (e.g. retinopathy) and CAN itself. Finally, we also are unable to assess the clinical impact of CAN without longitudinal observation of those with and without CAN, which we hope to explore in future studies. Finally, our estimates of relationships between CAN and correlates are susceptible to residual confounding of additional factors which we might not have measured or included in our regression models.

Conclusion

We detected CAN in over half of individuals with diabetes attending an outpatient diabetes clinic in Uganda. Older age, longer duration of diabetes, and co-existence of retinopathy were key correlates of the condition. Generally, our data highlight the need for better recognition of CAN as a common complication in diabetes. We therefore recommend that screening for CAN should be considered as part of routine evaluation of diabetic individuals in ambulatory care given the high prevalence of CAN in this study population and the rising burden of diabetes. This study also emphasizes the need for better management of diabetes including improved glycemic control and regular screening for other micro-vascular complications of diabetes such as retinopathy in diabetic individuals with CAN.

Data Accessibility Statements

The datasets generated and analyzed during the study are available from the corresponding author on request.

Abbreviations

aOR: Adjusted Odds Ratio, BMI: Body mass index, BP: Blood pressure, CAN: Cardiovascular autonomic neuropathy, CI: Confidence interval, ECG: Electrocardiogram, HbA1c: Glycosylated hemoglobin, HOMA: Homeostatic model assessment, HRV: Heart rate variability, IQR: Inter-quartile range, MET: Metabolic equivalent task, MRRH: Mbarara Regional Referral Hospital, MUST: Mbarara University of Science and Technology, NPDR: Non-proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy, PI: Postural Index, QTc: Heart rate corrected QT interval, SD: Standard deviation, T1DM: Type 1 diabetes mellitus, T2DM: Type 2 diabetes mellitus.

Ethics and Consent

The study was approved by the institutional ethics review board of Mbarara University of Science and Technology (MUST-REC). We also received clearance for the study from the Uganda National Council of Science and Technology (UNCST) and from the Research Secretariat in the Office of the President of Uganda, in accordance with the national guidelines. All study participants provided written informed consent before recruitment and participation. Participants who could not write gave consent with a thumbprint.

Acknowledgements

We thank the patients who participated in the study, the staff and management of Mbarara Regional Referral Hospital who contributed in various ways towards the success of the study. We are very grateful to members of the Technical Advisory Committee (TAC) of Mbarara University Research Training Initiative (MURTI) for their technical input into the study. We also acknowledge Dr. Sam Ruvuma of the Ophthalmology Department of Mbarara University of Science and Technology for his technical support.

Funding Information

This research was supported by the Fogarty International Center and co-founding partners (NIH Common Fund, Office of Strategic Coordination, Office of the Director (OD/OSC/CF/NIH); Office of AIDS Research, Office of the Director (OAR/NIH); National Institute of Mental Health (NIMH/NIH); and National Institute of Neurological Disorders and Stroke (NINDS/NIH)) of the National Institutes of Health under Award Number D43TW010128. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Competing Interests

The authors have no competing interests to declare.

Author Contributions

R.M., A.M., D.C.A., S.L.M., and M.S. conceived the study, contributed to discussion, and reviewed, edited and wrote the manuscript. R.T. and R.M. collected the data. G.K. and D.C.A. reviewed ECG recordings. R.M. and M.S. analyzed the data. T.K. performed direct ophthalmoscopy on study participants. R.M. is the guarantor of this research work and, as such, had full access to all the data for the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

References

1. **Organization WH.** Global Report on Diabetes: World Health Organization; 2016.
2. **Roglic G.** WHO Global report on diabetes: A summary. *International Journal of Noncommunicable Diseases.* 2016; 1(1): 3. DOI: <https://doi.org/10.4103/2468-8827.184853>
3. **Shaw JE, Sicree RA, Zimmet PZ.** Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Research and Clinical Practice.* 2010; 87(1): 4–14. DOI: <https://doi.org/10.1016/j.diabres.2009.10.007>
4. **Whiting DR, Guariguata L, Weil C, Shaw J.** IDF diabetes atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Research and Clinical Practice.* 2011; 94(3): 311–21. DOI: <https://doi.org/10.1016/j.diabres.2011.10.029>
5. **Herman WH.** The Global Burden of Diabetes: An Overview. *Diabetes Mellitus in Developing Countries and Underserved Communities.* Springer. 2017; 1–5. DOI: https://doi.org/10.1007/978-3-319-41559-8_1
6. **Assah F, Mbanya JC.** Diabetes in Sub-Saharan Africa. *Diabetes Mellitus in Developing Countries and Underserved Communities.* Springer. 2017; 33–48. DOI: https://doi.org/10.1007/978-3-319-41559-8_3
7. **Spallone V, Ziegler D, Freeman R, Bernardi L, Frontoni S, Pop-Busui R,** et al. Cardiovascular autonomic neuropathy in diabetes: Clinical impact, assessment, diagnosis, and management. *Diabetes/Metabolism Research and Reviews.* 2011; 27(7): 639–53. DOI: <https://doi.org/10.1002/dmrr.1239>
8. **Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P,** et al. Diabetic neuropathies: Update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care.* 2010; 33(10): 2285–93. DOI: <https://doi.org/10.2337/dc10-1303>
9. **Balcioğlu AS, Müderrisoğlu H.** Diabetes and cardiac autonomic neuropathy: Clinical manifestations, cardiovascular consequences, diagnosis and treatment. *World Journal of Diabetes.* 2015; 6(1): 80. DOI: <https://doi.org/10.4239/wjd.v6.i1.80>
10. **Pop-Busui R.** What do we know and we do not know about cardiovascular autonomic neuropathy in diabetes. *Journal of Cardiovascular Translational Research.* 2012; 5(4): 463–78. DOI: <https://doi.org/10.1007/s12265-012-9367-6>

11. **Ewing DJ, Clarke BF.** Autonomic neuropathy: its diagnosis and prognosis. *Clinics in Endocrinology and Metabolism.* 1986; 15(4): 855–88. DOI: [https://doi.org/10.1016/S0300-595X\(86\)80078-0](https://doi.org/10.1016/S0300-595X(86)80078-0)
12. **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. DOI: <https://doi.org/10.2337/diacare.8.5.491>
13. **Valensi P, Paries J, Attali J, for Research FG.** Cardiac autonomic neuropathy in diabetic patients: influence of diabetes duration, obesity, and microangiopathic complications—the French multicenter study. *Metabolism.* 2003; 52(7): 815–20. DOI: [https://doi.org/10.1016/S0026-0495\(03\)00095-7](https://doi.org/10.1016/S0026-0495(03)00095-7)
14. **Ziegler D, Gries F, Mühlen H, Rathmann W, Spüler M, Lessmann F.** Prevalence and clinical correlates of cardiovascular autonomic and peripheral diabetic neuropathy in patients attending diabetes centers. The Diacan Multicenter Study Group C. *Diabete & Metabolisme.* 1993; 19(1 Pt 2): 143–51.
15. **Vinik AI, Maser RE, Mitchell BD, Freeman R.** Diabetic autonomic neuropathy. *Diabetes care.* 2003; 26(5): 1553–79. DOI: <https://doi.org/10.2337/diacare.26.5.1553>
16. **Association AD.** Physical activity/exercise and diabetes. *Diabetes Care.* 2004; 27(suppl 1): s58–s62. DOI: <https://doi.org/10.2337/diacare.27.2007.S58>
17. **Maser RE, Mitchell BD, Vinik AI, Freeman R.** The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes. *Diabetes Care.* 2003; 26(6): 1895–901. DOI: <https://doi.org/10.2337/diacare.26.6.1895>
18. **Maser RE, Mitchell BD, Vinik AI, Freeman R.** The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. *Diabetes Care.* 2003; 26(6): 1895–901. DOI: <https://doi.org/10.2337/diacare.26.6.1895>
19. **Jin J, Wang W, Zhu L, Gu T, Niu Q, Li P, et al.** Cardiovascular autonomic neuropathy is an independent risk factor for left ventricular diastolic dysfunction in patients with type 2 diabetes. *BioMed Research International.* 2017; 2017. DOI: <https://doi.org/10.1155/2017/3270617>
20. **Howorka K, Pumprla J, Haber P, Koller-Strametz J, Mondrzyk J, Schabmann A.** Effects of physical training on heart rate variability in diabetic patients with various degrees of cardiovascular autonomic neuropathy. *Cardiovascular Research.* 1997; 34(1): 206–14. DOI: [https://doi.org/10.1016/S0008-6363\(97\)00040-0](https://doi.org/10.1016/S0008-6363(97)00040-0)
21. **Organization WH.** Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. *Report of a WHO/IDF consultation;* 2006.
22. **Association AD.** Standards of medical care in diabetes—2012. *Diabetes Care.* 2012; 35: S11. DOI: <https://doi.org/10.2337/dc12-s011>
23. **Chamberlain JJ, Rhinehart AS, Shaefer CF, Neuman A.** Diagnosis and management of diabetes: Synopsis of the 2016 American diabetes association standards of medical care in diabetes. *Annals of Internal Medicine.* 2016; 164(8): 542–52. DOI: <https://doi.org/10.7326/M15-3016>
24. **Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr, et al.** Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension.* 2003; 42(6): 1206–52. DOI: <https://doi.org/10.1161/01.HYP.000107251.49515.c2>
25. **Health NIO.** Classification of overweight and obesity by BMI, waist circumference, and associated disease risks; 2016.
26. **National CEPN.** Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report. *Circulation.* 2002; 106(25): 3143. DOI: <https://doi.org/10.1161/circ.106.25.3143>
27. **Armstrong T, Bull F.** Development of the world health organization global physical activity questionnaire (GPAQ). *Journal of Public Health.* 2006; 14(2): 66–70. DOI: <https://doi.org/10.1007/s10389-006-0024-x>
28. **Jeppsson J-O, Kobold U, Barr J, Finke A, Hoelzel W, Hoshino T, et al.** Approved IFCC reference method for the measurement of HbA1c in human blood. *Clinical Chemistry and Laboratory medicine.* 2002; 40(1): 78–89. DOI: <https://doi.org/10.1515/CCLM.2002.016>
29. **Ward D.** Prolongation of the QT interval as an indicator of risk of a cardiac event. *European Heart Journal.* 1988; 9: 139–44. DOI: https://doi.org/10.1093/eurheartj/9.suppl_G.139
30. **Ahnve S.** Correction of the QT interval for heart rate: Review of different formulas and the use of Bazett's formula in myocardial infarction. *American Heart Journal.* 1985; 109(3): 568–74. DOI: [https://doi.org/10.1016/0002-8703\(85\)90564-2](https://doi.org/10.1016/0002-8703(85)90564-2)

31. **Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R**, et al. Diabetic neuropathies: A statement by the American diabetes association. *Diabetes Care*. 2005; 28(4): 956–62. DOI: <https://doi.org/10.2337/diacare.28.4.956>
32. **Kuehl M, Stevens MJ**. Cardiovascular autonomic neuropathies as complications of diabetes mellitus. *Nature Reviews Endocrinology*. 2012; 8(7): 405. DOI: <https://doi.org/10.1038/nrendo.2012.21>
33. **Bellavere F, Bosello G, Fedele D, Cardone C, Ferri M**. Diagnosis and management of diabetic autonomic neuropathy. *British Medical Journal (Clinical Research Ed)*. 1983; 287(6384): 61. DOI: <https://doi.org/10.1136/bmj.287.6384.61-a>
34. **Jung C-H, Kim B-Y, Kim C-H, Kang S-K, Jung S-H, Mok J-O**. Association of serum adipocytokine levels with cardiac autonomic neuropathy in type 2 diabetic patients. *Cardiovascular Diabetology*. 2012; 11(1): 24. DOI: <https://doi.org/10.1186/1475-2840-11-24>
35. **Jyotsna VP, Singh AK, Deepak K, Sreenivas V**. Progression of cardiac autonomic dysfunction in newly detected type 2 diabetes. *Diabetes Research and Clinical Practice*. 2010; 90(1): e5–e6. DOI: <https://doi.org/10.1016/j.diabres.2010.04.009>
36. **Khandelwal E, Jaryal AK, Deepak KK**. Pattern and prevalence of cardiovascular autonomic neuropathy in diabetics visiting a tertiary care referral center in India. *Indian J Physiol Pharmacol*. 2011; 55(2): 119–27.
37. **Pappachan J, Sebastian J, Bino B, Jayaprakash K, Vijayakumar K, Sujathan P**, et al. Cardiac autonomic neuropathy in diabetes mellitus: prevalence, risk factors and utility of corrected QT interval in the ECG for its diagnosis. *Postgraduate Medical Journal*. 2008; 84(990): 205–10. DOI: <https://doi.org/10.1136/pgmj.2007.064048>
38. **Gandhi AU, Patel HP, Patel SV, Kadam AY, Parmar VM**. Cardiac autonomic neuropathy in relation to cardiovascular reflex tests and QTc prolongation in diabetes mellitus. *National Journal of Integrated Research in Medicine*. 2017; 8(4).
39. **Eze C, Onwuekwe I, Ogunniyi A**. The frequency and pattern of cardiac autonomic neuropathy (CAN) in type 2 DM patients in a diabetic clinic in Enugu south-east Nigeria. *Niger J Med*. 2013; 22(1): 24–31.
40. **Jaiswal M, Divers J, Urbina EM, Dabelea D, Bell RA, Pettitt DJ**, et al. Cardiovascular autonomic neuropathy in adolescents and young adults with type 1 and type 2 diabetes: The SEARCH for diabetes in youth cohort study. *Pediatric Diabetes*. 2018; 19(4): 680–9. DOI: <https://doi.org/10.1111/pedi.12633>
41. **Ratzmann KP, Raschke M, Gander I, Schimke E**. Prevalence of peripheral and autonomic neuropathy in newly diagnosed type II (noninsulin-dependent) diabetes. *Journal of Diabetic Complications*. 1991; 5(1): 1–5. DOI: [https://doi.org/10.1016/0891-6632\(91\)90002-7](https://doi.org/10.1016/0891-6632(91)90002-7)
42. **Zoppini G, Cacciatori V, Raimondo D, Gemma M, Trombetta M, Dauriz M**, et al. The prevalence of cardiovascular autonomic neuropathy in a cohort of patients with newly diagnosed type 2 diabetes: the Verona newly diagnosed type 2 diabetes study (VNDS). *Diabetes Care*. 2015; dc150081. DOI: <https://doi.org/10.2337/dc15-0081>
43. **Ziegler D, Dannehl K, Mühlen H, Spüler M, Gries F**. Prevalence of cardiovascular autonomic dysfunction assessed by spectral analysis, vector analysis, and standard tests of heart rate variation and blood pressure responses at various stages of diabetic neuropathy. *Diabetic Medicine*. 1992; 9(9): 806–14. DOI: <https://doi.org/10.1111/j.1464-5491.1992.tb01898.x>
44. **American Diabetes Association**. Standards of medical care in diabetes—2016. *Diabetes Care*. 2016; 39: 39–46. DOI: <https://doi.org/10.2337/dc16-S003>
45. **Vinik AI, Erbas T, Casellini CM**. Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. *Journal of Diabetes Investigation*. 2013; 4(1): 4–18. DOI: <https://doi.org/10.1111/jdi.12042>
46. **Rolim LCdSP, Sá JRd, Chacra AR, Dib SA**. Diabetic cardiovascular autonomic neuropathy: risk factors, clinical impact and early diagnosis. *Arquivos Brasileiros de Cardiologia*. 2008; 90(4): e24–e32. DOI: <https://doi.org/10.1590/S0066-782X2008000400014>
47. **Fisher VL, Tahrani AA**. Cardiac autonomic neuropathy in patients with diabetes mellitus: current perspectives. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*. 2017; 10: 419. DOI: <https://doi.org/10.2147/DMSO.S129797>
48. **Vinik AI, Ziegler D**. Diabetic cardiovascular autonomic neuropathy. *Circulation*. 2007; 115(3): 387–97. DOI: <https://doi.org/10.1161/CIRCULATIONAHA.106.634949>
49. **Refaie W**. Assessment of cardiac autonomic neuropathy in long standing type 2 diabetic women. *The Egyptian Heart Journal*. 2014; 66(1): 63–9. DOI: <https://doi.org/10.1016/j.ehj.2013.06.002>

50. **Ko S-H, Park S-A, Cho J-H, Song K-H, Yoon K-H, Cha B-Y**, et al. Progression of cardiovascular autonomic dysfunction in patients with type 2 diabetes: A 7-year follow-up study. *Diabetes Care*. 2008; 31(9): 1832–6. DOI: <https://doi.org/10.2337/dc08-0682>
51. **Huang C-C, Lee J-J, Lin T-K, Tsai N-W, Huang C-R, Chen S-F**, et al. Diabetic retinopathy is strongly predictive of cardiovascular autonomic neuropathy in type 2 diabetes. *Journal of diabetes research*. 2016; 2016. DOI: <https://doi.org/10.1155/2016/6090749>
52. **Krolewski AS, Barzilay J, Warram JH, Martin BC, Pfeifer M, Rand LI**. Risk of early-onset proliferative retinopathy in IDDM is closely related to cardiovascular autonomic neuropathy. *Diabetes*. 1992; 41(4): 430–7. DOI: <https://doi.org/10.2337/diab.41.4.430>
53. **Pavy-Le Traon A, Fontaine S, Tap G, Guidolin B, Senard J-M, Hanaire H**. Cardiovascular autonomic neuropathy and other complications in type 1 diabetes. *Clinical Autonomic Research*. 2010; 20(3): 153–60. DOI: <https://doi.org/10.1007/s10286-010-0062-x>
54. **Dimitropoulos G, Tahrani AA, Stevens MJ**. Cardiac autonomic neuropathy in patients with diabetes mellitus. *World Journal of Diabetes*. 2014; 5(1): 17. DOI: <https://doi.org/10.4239/wjd.v5.i1.17>
55. **Feldman EL, Nave K-A, Jensen TS, Bennett DL**. New horizons in diabetic neuropathy: mechanisms, bioenergetics, and pain. *Neuron*. 2017; 93(6): 1296–313. DOI: <https://doi.org/10.1016/j.neuron.2017.02.005>
56. **Sugimoto K, Yasujima M, Yagihashi S**. Role of advanced glycation end products in diabetic neuropathy. *Current Pharmaceutical Design*. 2008; 14(10): 953–61. DOI: <https://doi.org/10.2174/138161208784139774>
57. **Larsen JR, Sjøholm H, Berg TJ, Sandvik L, Brekke M, Hanssen KF**, et al. Eighteen years of fair glycemic control preserves cardiac autonomic function in type 1 diabetes. *Diabetes Care*. 2004; 27(4): 963–6. DOI: <https://doi.org/10.2337/diacare.27.4.963>
58. **Bonora E, Formentini G, Calcaterra F, Lombardi S, Marini F, Zenari L**, et al. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. *Diabetes Care*. 2002; 25(7): 1135–41. DOI: <https://doi.org/10.2337/diacare.25.7.1135>
59. **Witte D, Tesfaye S, Chaturvedi N, Eaton S, Kempler P, Fuller J**, et al. Risk factors for cardiac autonomic neuropathy in type 1 diabetes mellitus. *Diabetologia*. 2005; 48(1): 164–71. DOI: <https://doi.org/10.1007/s00125-004-1617-y>
60. **O'Brien I, O'Hare P, Corral R**. Heart rate variability in healthy subjects: Effect of age and the derivation of normal ranges for tests of autonomic function. *Heart*. 1986; 55(4): 348–54. DOI: <https://doi.org/10.1136/hrt.55.4.348>
61. **Esler M, Hastings J, Lambert G, Kaye D, Jennings G, Seals DR**. The influence of aging on the human sympathetic nervous system and brain norepinephrine turnover. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2002; 282(3): R909–R16. DOI: <https://doi.org/10.1152/ajpregu.00335.2001>
62. **Ewing D, Campbell I, Murray A, Neilson J, Clarke B**. Immediate heart-rate response to standing: simple test for autonomic neuropathy in diabetes. *Br Med J*. 1978; 1(6106): 145–7. DOI: <https://doi.org/10.1136/bmj.1.6106.145>
63. **Rowe JW, Troen BR**. Sympathetic nervous system and aging in man. *Endocrine Reviews*. 1980; 1(2): 167–79. DOI: <https://doi.org/10.1210/edrv-1-2-167>
64. **Bonnemeier H, Wiegand UK, Brandes A, Kluge N, Katus HA, Richardt G**, et al. Circadian profile of cardiac autonomic nervous modulation in healthy subjects: differing effects of aging and gender on heart rate variability. *Journal of Cardiovascular Electrophysiology*. 2003; 14(8): 791–9. DOI: <https://doi.org/10.1046/j.1540-8167.2003.03078.x>
65. **Valensi PE, Johnson NB, Maison-Blanche P, Extramania F, Motte G, Coumel P**. Influence of cardiac autonomic neuropathy on heart rate dependence of ventricular repolarization in diabetic patients. *Diabetes Care*. 2002; 25(5): 918–23. DOI: <https://doi.org/10.2337/diacare.25.5.918>
66. **Ninkovic VM, Ninkovic SM, Miloradovic V, Stanojevic D, Babic M, Giga V**, et al. Prevalence and risk factors for prolonged QT interval and QT dispersion in patients with type 2 diabetes. *Acta Diabetologica*. 2016; 53(5): 737–44. DOI: <https://doi.org/10.1007/s00592-016-0864-y>
67. **Vinik AI, Casellini C, Parson HK, Colberg SR, Nevoret M-L**. Cardiac autonomic neuropathy in diabetes: A predictor of cardiometabolic events. *Frontiers in Neuroscience*. 2018; 12. DOI: <https://doi.org/10.3389/fnins.2018.00591>

How to cite this article: Migisha R, Agaba DC, Katamba G, Kwaga T, Tumwesigye R, Miranda SL, Muyingo A, Siedner MJ. Prevalence and Correlates of Cardiovascular Autonomic Neuropathy Among Patients with Diabetes in Uganda: A Hospital-Based Cross-sectional Study. *Global Heart*. 2020; 15(1): 21. DOI: <https://doi.org/10.5334/gh.765>

Submitted: 04 February 2020

Accepted: 04 February 2020

Published: 02 March 2020

Copyright: © 2020 The Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC-BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. See <http://creativecommons.org/licenses/by/4.0/>.



Global Heart is a peer-reviewed open access journal published by Ubiquity Press.

OPEN ACCESS The Open Access icon, which is a stylized 'a' inside a circle.