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Prevalence of Cardiac Autonomic Neuropathy in Type-2 Diabetic Patients in Nigeria Assessed by Spectral Analysis of Heart Rate Variability

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ABSTRACT

Cardiac autonomic neuropathy (CAN) is a complication of diabetes mellitus (DM). It often remains undiagnosed progressing into fatal cardiovascular outcomes. This study aimed at investigating the prevalence of CAN in diabetic out-patients in southwestern Nigeria. It was a cross-sectional study approved (UI/EC/13/0374) and conducted at the University College Hospital, Ibadan, Nigeria. Informed consents were obtained from fifty volunteer type-2 diabetic patients. Heart rate (HR) and blood pressure of the patients were taken. Heart rate variability (HRV) was determined using Five minutes ECG subjected to power spectral density analysis. Fasting blood glucose (FBG) and plasma apolipoprotein (apo) B levels were determined via a glucometer and immunoturbidimetric assay respectively. Results were presented as frequencies or mean±SD where applicable. Binary logistic regression at CI= 95% was used to evaluate the predictors of CAN in DM at P= 0.05. Eighty-two percent of the patients had abnormal time and/or frequency spectra of HRV indicating CAN. Binary logistic regression analysis revealed that patient's age (Odds ratio [OR] =0.88, p=0.025), poor glycaemic control (OR=0.156, p=0.043), increased HR (OR= 3.72, p=0.042) and hypertension (OR=0.08, p=0.031) were significant predictors of CAN while Apo B was not significant. This study shows that there is a high prevalence of CAN which is asymptomatic and undiagnosed in type-2 diabetic patients, and dependent on risk factors such as poor glycaemic control, patient's age, hypertension and increased heart rate. Therefore, it is recommended that HRV be done routinely in DM patients for early detection of asymptomatic CAN and timely intervention so as to reduce cardiovascular related morbidity and mortality.

Keywords: Cardiac autonomic neuropathy (CAN), Heart rate variability (HRV), Apolipoprotein B, poor glycaemic control, Hypertension, type II diabetes

INTRODUCTION

The prevalence of diabetes mellitus has kept increasing globally over the years beyond projected estimates. It increased globally from 108 million (4.7%) in 1980 to 422 million (8.5%) in 2014 and to 463 million (9.3%) in 2019 [1,2], amounting to about 429% increase. Thus, over 9.3% of the world's population are living with diabetes as at today with over 99% of them having the type-2 diabetes and 79% of them living in middle- and low-income countries [2]. In Africa, over 19 million people, that is 4.7% of Africa's population are living with diabetes as at 2019, and 45 million adults already have impaired glucose tolerance [2]; thus, the prevalence of diabetes would continue to increase. In

Nigeria, the prevalence of diabetes is said to be 3% amounting to over 2.7 million people living with the condition [2,3]. A meta-analysis study estimated that the prevalence of diabetes is Nigeria varies between 0.65% in rural and 11.0% in urban areas with the greatest prevalence in Southwestern Nigeria [4]. With the incidence of diabetes, diabetic complications are also expected to rise proportionately. Diabetes, with its associated complications, is estimated to be the cause of 11.3% of deaths globally with 46.2% of the deaths attributable to diabetics under the age of 60 years, out of which Africa contributes the highest (33.8%) [2]. Diabetic neuropathy (DN) is the most common microvascular complication of diabetes and is the main cause of neuropathy in the world [5]. It results from microvascular injury involving small blood vessels that supply nerves and, sometimes, macrovascular pathogenesis may be involved [6]. The pathogenesis of neuropathy in type II diabetes is multifactorial and related to metabolic disturbances such as hyperglycaemia, dyslipidaemia, oxidative and nitrosative stress, all of which result in nerve injury [7]. Autonomic nervous system imbalance manifests as cardiovascular autonomic neuropathy (CAN) which is one of the most common manifestations of DN and is an independent predictor of myocardial infarction and cardiovascular death [8]. Also, diabetic patients have two- to three- fold increased risk of heart attacks and strokes leading to increased morbidity as a result of CAN [9]. The autonomic nervous system (ANS) is a major regulator of the cardiovascular system. It regulates heart rate and blood pressure in the short-term regulatory mechanism to cope with everyday situations. Thus, autonomic nervous system dysfunction, which is one of the significant complications of diabetes mellitus, is the cause of cardiac autonomic neuropathy [10]. CAN is asymptomatic and thus un-diagnosed until in its late stage when it must have resulted in life threatening complications such as arrhythmias, silent myocardial ischemia, and sometimes sudden death. Additionally, it is related with other microangiopathic co-morbidities and, as such, has been described as a silent killer [11, 12]. Therefore, early diagnosis of cardiac autonomic dysfunction is important. Cardiac autonomic neuropathy can be detected very early, long before it starts presenting symptoms, using Heart rate variability (HRV). However, HRV is not one of the routine examinations done on diabetic patients attending diabetic clinics in Nigeria. That being the case, the presence of CAN is not often detected until it has led to fatal cardiovascular morbidity and mortality. Thus, this study was conducted to determine the prevalence of CAN among type 2 diabetic patients attending a clinic in the South-western part of Nigeria. The study also seeks to determine the risk factors which significantly influences the prevalence of CAN.

MATERIALS AND METHODS

Type 2 diabetic patients who volunteered were recruited for the study after an informed consent and approval. The patient's demographic characteristics such as age, sex, history of diabetes, lifestyle *etcetera* was obtained through a questionnaire. In addition, clinical records of subjects were used to ascertain information such as age of diabetes, drugs and treatment history, mental state, infections, seizures, complications and presence of other chronic conditions, to determine eligibility.

Ethical considerations

This study was approved by the ethical committee of the University College Hospital (UCH), Ibadan, and assigned the number UI/EC/13/0374. Participants were properly briefed about the study and their consent taken in written form before they were enrolled into the study. Only those who gave their consent were enrolled in the study. Confidentiality of participants' information was ensured with the use of numbers assigned to the patients. Participants were treated with utmost respect, their privacy protected, their wellbeing closely monitored, and were informed that they could voluntarily withdraw from the study at any time if they so desired.

Study design: This study was cross sectional in design.

Study site: Out-patient diabetic clinic, UCH, Ibadan, Nigeria

Sample size: Fifty volunteers were recruited for the study

Sampling technique: Type 2 diabetic patients were recruited for this study via purposive sampling technique.

Inclusion criteria: Consenting subjects diagnosed with type 2 diabetes aged 30 years and above.

Volume 3, Issue 6; November-December 2020; Page No 552-560

Exclusion criteria: The following were excluded from the study: type 1 diabetics (i.e less than 30years old and insulin dependent); Diabetic subjects with presence of other chronic conditions or symptoms of neuropathy or with other infections; subjects with previous history of myocardial infarction, ischemic heart disease, renal disease and patients on specific drugs (with adverse effect on autonomic functions) that can interfere with the study; Non consenting participants.

Outcome measures

Cardiac autonomic function tests: Baseline ECG, heart rate and BP of patients were measured. Blood pressure was measured using a sphygmomanometer. Heart rate was determined using the ECG in a supine position. Heart rate variability (HRV) was done with five minutes continuous ECG subjected to power spectral density analysis to assess cardiac autonomic function.

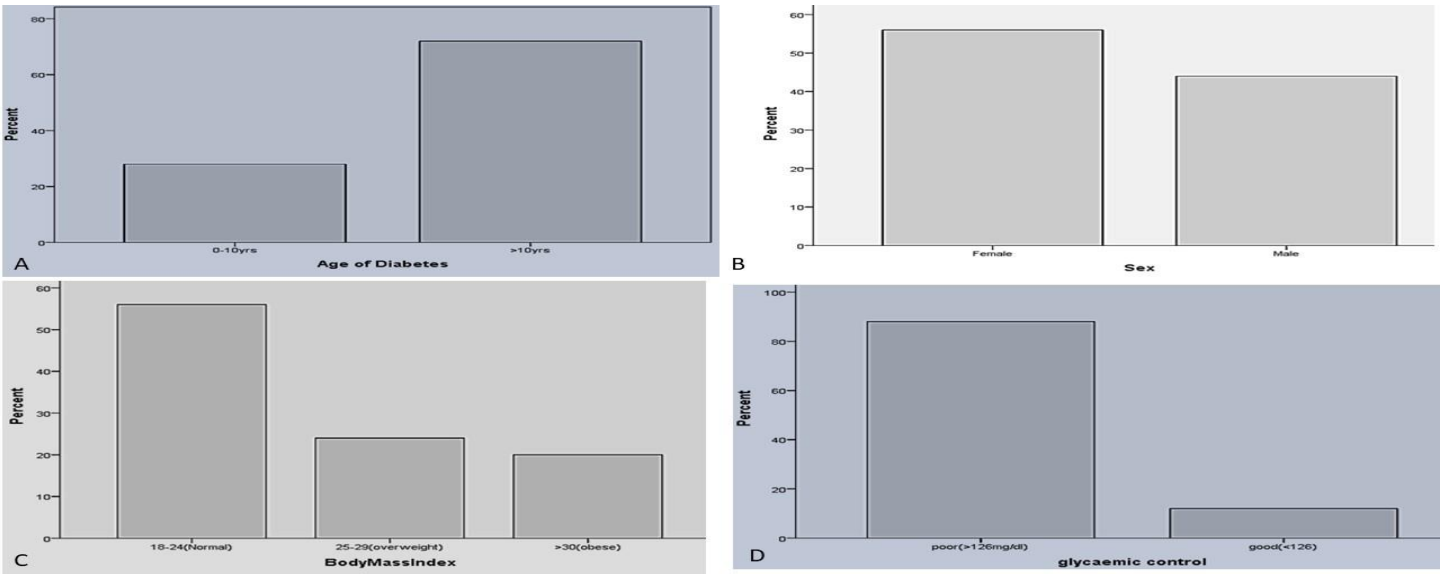
Fasting blood glucose (FBG) measurement: This was done using a glucometer

Blood collection method: Five millilitres of blood was collected from the cubital fossa using a 5ml needle and syringe. Apolipoprotein B content of the serum was assayed immunoturbidimetrically.

Data analysis method: Results were presented as frequencies or mean ± SD where applicable. Binary logistic regression technique was employed in 'SPSS version 23' to determine risk factors of CAN. A *p* value of 0.05 was taken as statistical significance of difference.

Results

The study included a total of fifty type II diabetic patients aged between 30 and 80 years with a mean diabetes age of 15.8 ± 9.4 years (Table 1). The distribution of the patients according to diabetic age, sex and body mass index is shown in figure 1. More than half of the patients were females (56%, n=28) while 44% of them had poorly controlled hyperglycaemia (figure 1). The mean body mass index (BMI) of the patients was 25.8 ±3.8 (table 1) with 20% of them obese and 32% of them overweight (figure 1). The square root of the mean squared differences of successive NN intervals (RMSSD) and the Standard deviation of all NN intervals (SDNN) of the time domain power spectral density analysis of the heart rate variability of the patients are shown in figure 2. Also, forty-five percent of the patients had blood pressure greater than 140/90mmHg as shown in figure 2. The frequency domain parameters are shown in figure 3. Eighty-four percent of the patients had reduced total power (TP) as shown in figure 3. In all, eighty-two percent of the patients had two or more abnormal time and/or frequency domain parameters and these are said to have CAN. Of these, 32% had the early stage of CAN while 52% has established CAN (figure 4 and table 4). Resting heart rate of the patients are shown in table 2. Binary logistic regression analysis revealed that patient age, poor glycaemic control, increased heart rate and hypertension were significant risk factors of CAN while apolipoprotein B was not significant (tables 3 - 4).



Volume 3, Issue 6; November-December 2020; Page No 552-560

Figure 1. A). Percentage frequency of the diabetic age of the patients. B). Percentage frequency of the sex distribution of the type II diabetic patients. C). Body mass index of the patients showing normal, overweight and obese distributions. D). Percentage distribution of patients according to their Glycaemic control (CI=95%).

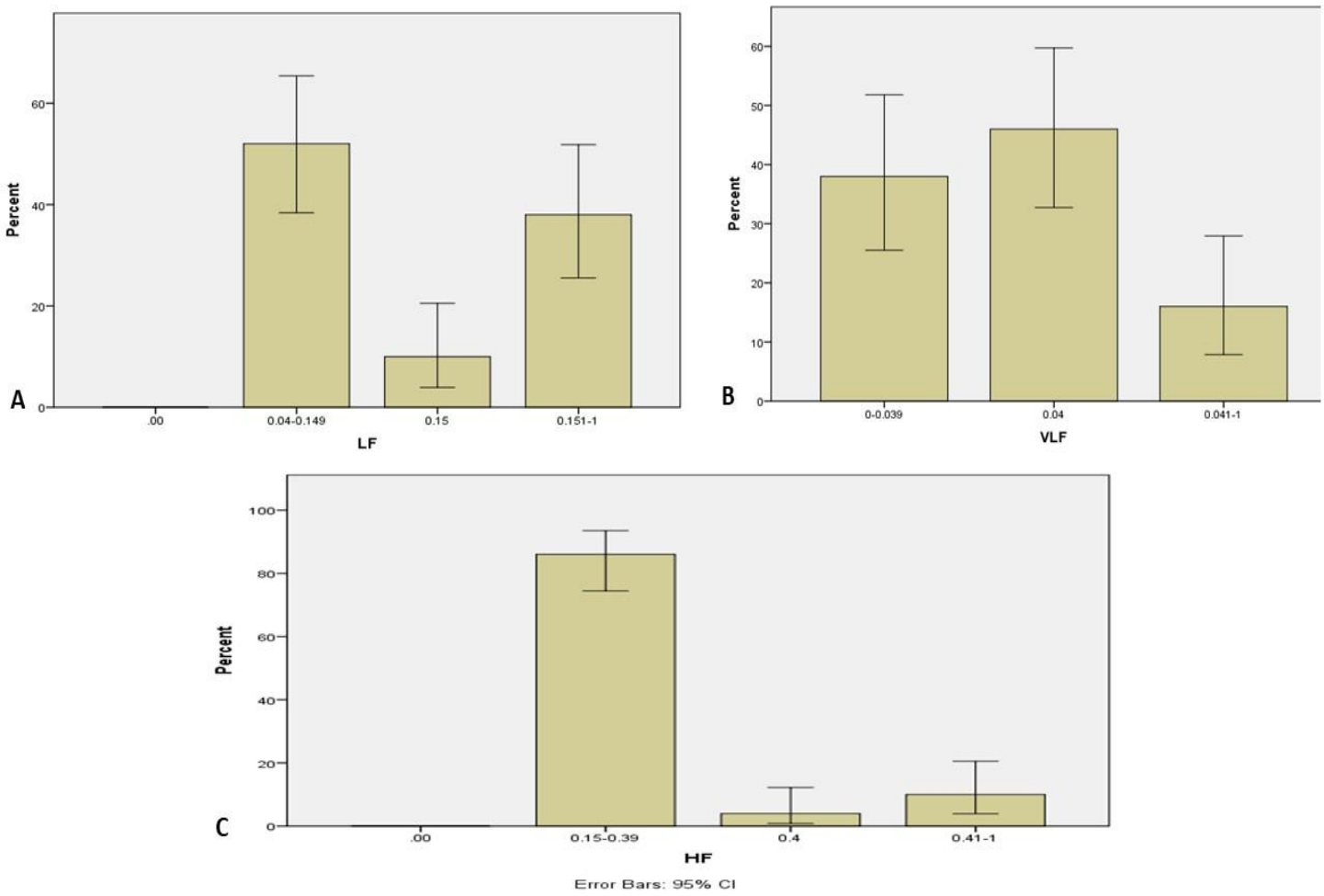


Figure 2: A) Hypertension in type II diabetic patients. B) The square Root of the Mean of the Sum of the Squares of Differences between adjacent NN interval (R-R interval) [RMSSD] of type II diabetic patients. C)Standard deviation of all NN intervals (SDNN) of type II diabetic patients.

Table 1: Summary of the characteristics of type II diabetic patients in the study

	N	Range	Minimum	Maximum	Mean	Std. Deviation
Patientage	50	30	50	80	65.16	7.369
Diabetes_age	50	33	2	35	15.78	9.494
BMI	50	15.7	18.4	34.0	25.829	3.8254
ApoB	50	41	129	169	149.99	13.021
FBG	50	153	98	251	177.38	43.922
Valid N (listwise)	50					

Volume 3, Issue 6; November-December 2020; Page No 552-560

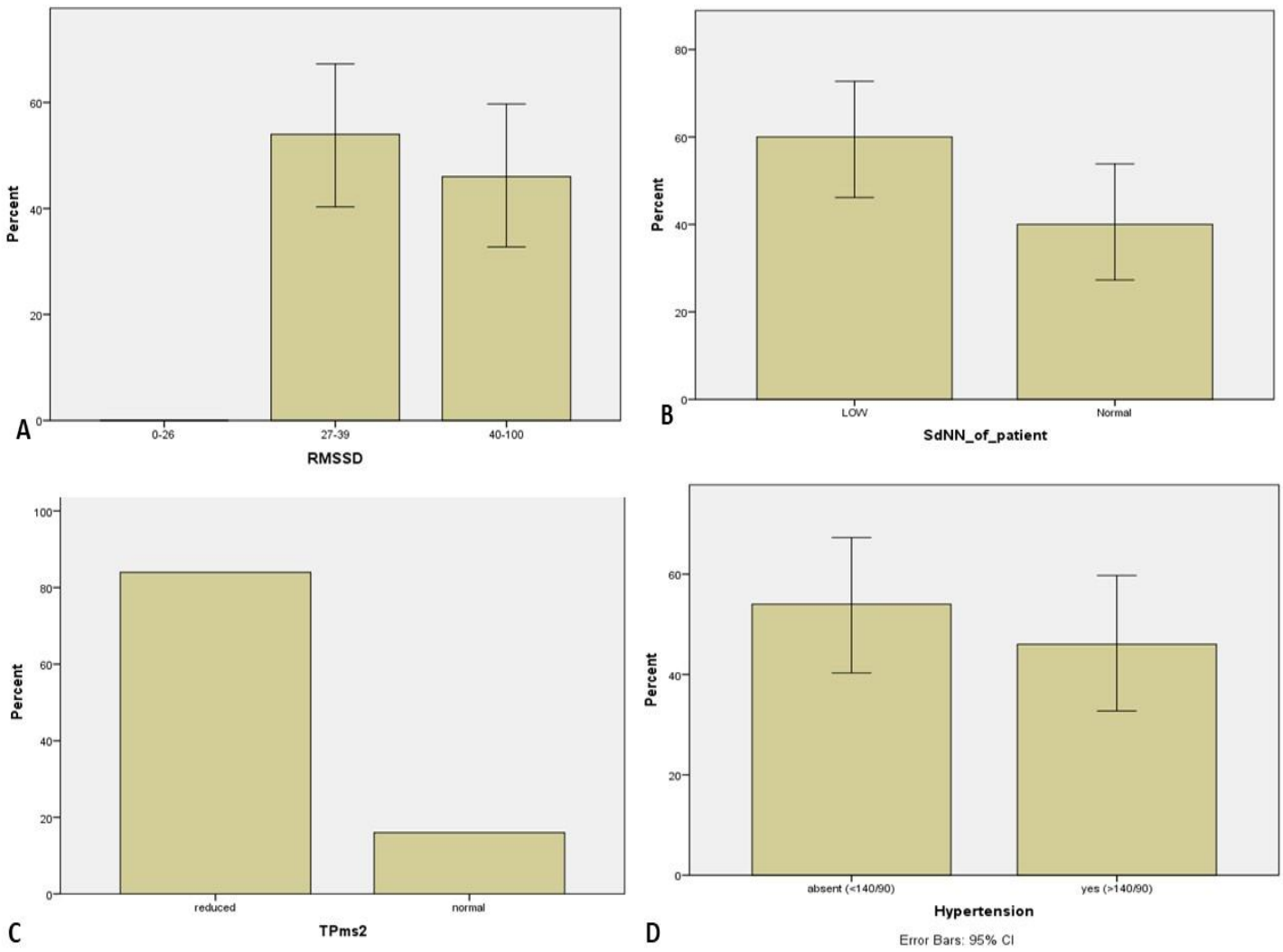


Figure 3: A). High frequency of the Heart rate variability of type II diabetic patients. B) Very low frequency of the heart rate variability of type II diabetic patients. C) Low frequency of the heart rate variability of type II diabetic patients. D) Total power of the heart rate variability of type II diabetic patients

Table 2: Resting Heart rate of diabetic patients

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Normocardia(50-89)	31	62.0	62.0	62.0
	Borderline(90-99)	13	26.0	26.0	88.0
	Tachycardia(100-200)	6	12.0	12.0	100.0
	Total	50	100.0	100.0	

Volume 3, Issue 6; November-December 2020; Page No 552-560

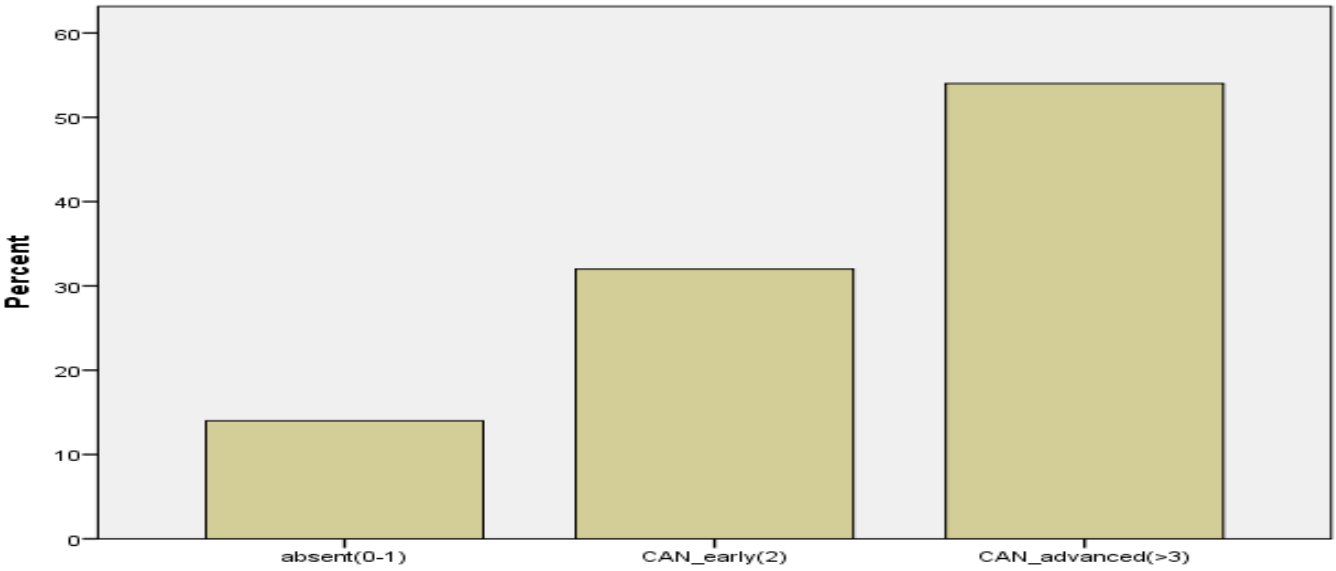


Figure 4: Prevalence of CAN in type II diabetic patients

Table 3: Binary logistics output of the presence of CAN in type II diabetic patients

			Predicted		
			CAN		
	Observed		absent(<II)	CAN_present(>II)	Percentage Correct
Step 1	CAN	absent(<II)	4	7	36.4
		CAN_present(>II)	2	37	94.9
	Overall Percentage				82.0

Table 4: Binary logistic analysis showing the significant predictors of CAN

A

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	HR	1.315	.648	4.122	1	.042	3.726	1.047	13.262
	Hypertension(1)	-2.528	1.169	4.677	1	.031	.080	.008	.789
	ApoB	-.030	.032	.926	1	.336	.970	.912	1.032
	HR_LN	-93.492	46.746	4.000	1	.046	.000	.000	.154
	Constant	311.581	153.359	4.128	1	.042	2.079E+135		

a. Variable(s) entered on step 1: HR, Hypertension, ApoB, HR_LN.

B

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Patient age	-.128	.057	5.011	1	.025	.880
	Glycaemic control	-1.857	.916	4.106	1	.043	.156
	Constant	11.052	4.118	7.201	1	.007	63046.6

a. Variable(s) entered on step 1: Patientage, Glycaemic_control. CI (95%)

DISCUSSION AND CONCLUSIONS

Volume 3, Issue 6; November-December 2020; Page No 552-560

This cross-sectional study evaluated the prevalence of cardiac autonomic neuropathy (CAN) and its associated risk factors in type II diabetic patients attending the University College Hospital, Ibadan, Nigeria. The study revealed a high prevalence of CAN diagnosed with power spectral density HRV as 82% of the patients met the criteria for CAN (score≥2), out of which 32% have early CAN (score=2) while 54% of the patients have definite CAN (score ≥ 3) [13] although asymptomatic. The prevalence of 54% for definite CAN in this study is close to that found in the study of Vinik *et al* which is 65% but greater than the prevalence earlier done in Nigeria by Eze *et al* and Bello *et al*. [14, 15, 16]. The prevalence of cardiac autonomic neuropathy can be as high as 90% depending on the diagnostic methods [15]. Bello et al [16] and Eze et al [14] reported a CAN prevalence of 46.3% and 44.3% respectively in DM patients in different parts of Nigeria. The differences in their study and this study could be attributed to methods of diagnosing CAN. They used some or all of the five traditional Ewing battery of tests which require a high level of the patient's cooperation and education. In addition, the power spectra density of HRV is one of the most sensitive, standardised and less cumbersome techniques for detecting CAN [17,18,19]. The early stage of CAN may not be detected by the Ewing battery cardiac autonomic reflex tests; however, this has been detected by HRV and confirmed using cardiac imaging and scintigraphy [20]. Thus, early asymptomatic CAN can only be detected by indices of spectral HRV [15]. It is important that CAN be detected early, so it can be treated, because it is one of the most insidious and disabling complications of DM in terms of quality of life and life expectancy [17].

The spectral density of HRV employs oscillations of RR intervals between consecutive heart beats as a function of autonomic nervous activities on the sinus node of the heart and presented in time and frequency domains [17]. In this study, both frequency and time domain of HRV were reduced in most of the diabetic patients. This indicates that they have impaired autonomic nervous system (ANS) modulation of heart rate, which heralds the development of cardiac autonomic neuropathy in them [19]. This has been reported to be strongly associated with increased risk of myocardial ischemia and sudden death.

The binomial logistic regression found that patient's age, poor glycaemic control, hypertension and increased heart rate are significant predicting factors for the presence of CAN in diabetic patients. This has been corroborated by some studies [13,16,21]. Diabetic patients with increased age and duration of diabetes are more predisposed to developing CAN [15] with the mortality rate in patients with CAN rating 5-6 times higher in the period of 5-6 years than the mortality in patients with diabetes but without CAN in the same period [13].

The mean patient age in this study was 65.2 years which may also account for the high prevalence of CAN observed in the study. Diabetes in patients over 50 years of age has been found to correlate with CAN [22]. This is because of age-related neuronal attrition which affects the functions of the autonomic nervous system, thus predisposing diabetic patients that are advanced in age to CAN [15]. Since many people with diabetes do not get themselves diagnosed early until they are well advanced in age and their diabetes is advanced, it is, therefore,8 needful to screen elderly or older (>50years) diabetic patients for CAN as soon as possible.

There is an established correlation between CAN and poor glycaemic control [22,23]. Early and intensive glucose control reduces the prevalence of CAN [24,15]. However, the prevalence of diabetic complications such as CAN in Nigeria continues to rise as a result of poor management of diabetic patients with only about a third of them achieving optimum targets of glycaemic control and blood pressure lowering [25,26]

High blood pressure and increased heart rate (tachycardia) are strong predictors of definite and advanced CAN as also shown by some studies [23,21]. High blood pressure indicates that there is sympathetic dominance and thus autonomic imbalance. This study revealed that DM patients with increased heartrate are about 3.6 times more likely to have CAN. Resting tachycardia is said to be a clinical manifestation of severe CAN [15,19]. In this study about 38% of the diabetic patients already have resting heart rate greater than 90-100bpm which is indicative of severe CAN. Apolipoprotein B is a better marker of low densities lipoproteins and atherogenic lipids than LDL-cholesterol. Studies have established correlation between CAN and lipid

Volume 3, Issue 6; November-December 2020; Page No 552-560

profiles such as LDL, cholesterol and triglyceride. However, this study found no significant correlation between apolipoprotein B and CAN. This may mean that CAN is independent of dyslipidaemia and may occur in its absence. This can be explained by the fact that CAN exists in patients with type 1 diabetes as this type of diabetes does not involve lipid disorders or obesity [21].

Conclusion

There is a very high prevalence of CAN in Nigeria and this could be due to age, increased heart rate, poor glycaemic control and high blood pressure and may not necessarily be dependent on dyslipidaemia. CAN is insidious, asymptomatic, and it reduces the quality of life of diabetic patients and leads to major cardiovascular events such as arrhythmias and myocardial infarction among others. Thus, it increases cardiovascular morbidity and mortality in diabetic patients. Therefore, there is need for screening asymptomatic patients for CAN using the spectral analysis HRV (based on 5mins ECG) at the point of diagnosis of diabetes and routinely, especially in older patients, so that it can be detected early and properly managed. Also, patients with hyperglycaemia but` without dyslipidaemia should be screened for CAN as it may be present without dyslipidaemia. Finally, there is need to improve on the management of diabetic patients in the country so as to achieve optimum glycaemic control and lowering of blood pressure in order to reduce the prevalence of CAN.

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Volume 3, Issue 6; November-December 2020; Page No 552-560

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Volume 3, Issue 6; November-December 2020; Page No 552-560