Original Article

The Frequency and Pattern of Cardiac Autonomic Neuropathy (CAN) in Type 2 DM Patients in a Diabetic Clinic in Enugu South-East Nigeria

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ABSTRACT
STUDY OBJECTIVES: To determine the frequency, pattern and grades of cardiac autonomic neuropathy (CAN) in type 2 diabetic patients in a diabetes mellitus (DM) clinic in Enugu South-East Nigeria.
METHODS: A cross sectional study of seventy (70) type 2 diabetic patients attending a DM clinic in Enugu South-East Nigeria was carried out. Cardiac autonomic function was determined using a battery of 5 non-invasive tests which include; Heart rate response (HRR) to Valsalva manoeuvre, HRR to deep breathing, HRR to standing, Resting heart rate, and Blood pressure (BP) response to standing.
RESULTS: The frequency of cardiac autonomic neuropathy (CAN) in type 2 diabetic patients was 44.3%. Resting tachycardia was the most specific, HRR to Valsalva manoeuvre was most sensitive while BP response to standing had the best positive predictive value in detecting cardiac autonomic neuropathy.
CONCLUSIONS: Cardiac autonomic neuropathy is a common complication in type 2 Diabetes Mellitus patients seen at Enugu. It is therefore recommended that Autonomic function test s be part of the standard care of type 2 diabetic patients and appropriate management instituted for both primary and secondary prevention.
KEY WORDS: Frequency, Cardiac Autonomic Neuropathy, Diabetes mellitus, Enugu, South-East Nigeria

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INTRODUCTION AND LITERATURE REVIEW

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycaemia.[1] It currently assumes a pandemic status, with global prevalence of 366 million in 2011 and expected rise to 552 million by 2030.[2] It is the 2nd most common non-communicable disease in Nigeria.[3]

Autonomic dysfunction is a serious and common complication of DM.[4] Cardiac autonomic neuropathy (CAN) is the most studied clinically important form of diabetic autonomic neuropathy (DAN). Meta-analysis of published data demonstrate that CAN as measured by heart rate variability (HRV) is strongly associated with increased risk of silent myocardial infarction and mortality.[4]
The reported prevalence of CAN varies, depending on the cohort studied or the methods used.[4] To address above, the 1988 San Antonio Conference on diabetic neuropathy recommended that each laboratory should standardize the objective measures using their own population norms, reporting both absolute data and the relationship of the data to the appropriate normative control population.[4]

In a community based study of diabetic neuropathy in Oxford, England, the prevalence of CAN as defined by one or more heart rate variability (HRV) test result was 16.7%.[5] In a further study, Zieger et al reported prevalence of 25.3% and 34.3% in the type 1 and type 2 DM patients respectively.[6]

In Nigeria, there are limited studies of CAN. Ofoegbu[7] reported 12.4% hospital prevalence of diabetic CAN in 1992 while Ukpabi[8] reported 29% in 2001 both at Enugu Nigeria. Ofoegbu[7] used abnormal HRV to Valsalva manoeuvre as evidence of CAN. Odusan et al[9] reported a 34.2% hospital prevalence rate in 2008 at Sagamu Nigeria and they defined it as presence of =3 abnormal HRV to Valsalva manoeuvre, deep breathing, standing, QTc interval and BP response to standing and hand grip. Ugoya et el[10] reported 75% hospital prevalence for diabetic peripheral neuropathy in 2006 at Jos. There could be theoretical possibility of rising prevalence of CAN due to improved diabetes care and increased longevity of the diabetic patients.

This study was conducted to determine the frequency and pattern of Cardiac Autonomic Neuropathy (CAN) in in Type 2 DM patients in a Diabetic clinic in Enugu South-East Nigeria.

PATIENTS AND METHODOLOGY

The study was carried out in the DM Clinic of University of Nigeria Teaching Hospital (UNTH) Enugu between July and October 2011. UNTH receives referral from the states within south east zone of Nigeria (Enugu, Ebonyi, Abia, Anambra, and Imo states) and the neighboring states (Kogi, Benue, Delta, and Cross-River States).

The study was cross-sectional, hospital based, descriptive and analytical.

The sample size was calculated using the WHO formula for sample size determination in a finite population as shown below and the result was multiplied by 2 and rounded off to the nearest ten in order to increase the

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reliability of the results. The obtained value was 70.
$n = Z^2pq/d^2$
where
n = minimum sample size
Z= standard deviation at confidence interval (1.96)
p=the prevalence of DM (2.2%)
q= 1-p
d= sampling error tolerated (5%)

Eligible and consenting type 2 diabetes mellitus patients of both sexes between the ages of 15-70yrs were drawn using systematic random sampling method ie first of every ten (10) patients seen at the UNTH diabetic clinic from July to October 2011

Ethical clearance was obtained from ethics committee of the UNTH Enugu.

A written consent was obtained after a detailed explanation of the procedures involved. For those that were illiterates, thumb printing was used.

The patients with the following conditions were excluded from the study:

- Chronic alcoholics with alcohol consumption of >120gm/wk
- Age >70yrs or <15yrs
- Subjects with chest disorders that may limit their ability to perform Valsalva manoeuvre
- History of prolonged recumbency
- Use of drugs known to affect autonomic nerves functions e.g. Beta blockers, tricyclic antidepressants, isoniazid, vincristine, oral nitrates.
- Chronic kidney disease (eGFR<60ml/min)
- Congestive cardiac failure
- Atrial fibrillation
- Parkinson's disease and other multi system atrophy
- Vagotomy
- Disorders causing tissue sclerosis e.g. systemic sclerosis
- Chronic liver disease
- Leprosy
- Goitre
- Severe anaemia

The withdrawal criteria were unwillingness to participate and inability to perform any of the manoeuvres.

PROCEDURE

Structured pre-tested questionnaires were administered to the eligible and consenting patients by the investigator. It assessed history of diabetes mellitus including duration of DM, level of control and symptoms of autonomic neuropathy like postural dizziness, erectile dysfunction, bowel habit, abnormal sweating etc.

Anthropometric data were obtained (height, weight, waist circumference, hip circumference) using stadiometer, weighing scale and measuring tape.

Autonomic neuropathy was then assessed using the modified Ewing and Clarke's method used by Demir et al[11] which consists of five tests namely;

- Resting tachycardia
- Heart rate response (HRR) to Valsalva manoeuvre.
- HRR to deep breathing.
- HRR to standing.
- Blood pressure response to standing.[12]

The parasympathetic function was assessed using resting tachycardia, HRR to Valsalva manoeuvre, HRR to deep breathing and HRR to standing while the sympathetic function was assessed using blood pressure response to standing.[12]

Electrocardiograph machine (model: ECG-1101, version: C) was used to assess resting heart rate, using rhythm strip (Lead II).

Then, another continuous ECG monitoring was done while the patient was sitting down and forcibly blowing into a mouth-piece (10ml syringe without needle) connected to a sphygmomanometer maintaining a pressure of 40mmHg for 15 seconds.[13] This was repeated for three times with one minute interval between them. Valsalva ratio, which is the ratio of the longest R-R interval after the manoeuvre and the shortest R-R interval during the manoeuvre, was calculated for each manoeuvre and the average used as the final value.[12]

More so, the patient took deep breaths regularly at a rate of 6 breaths per minute while sitting up (5 seconds in and 5 seconds out for each cycle) for 1 minute. A continuous ECG monitoring was recorded throughout the period using a marker to note onset of each inspiration and expiration. The difference between the maximum and minimum heart rate was calculated for each of the cycles and average taken as the final value.[12]

Furthermore, the patient stood from a supine position while the ECG was recorded. The point of starting to stand was marked on the ECG paper. The ratio of the longest R-R interval around the 30^{th} beat to that of the shortest R-R interval around the 15^{th} beat after the point of starting to stand was recorded.[12]

Finally, the supine blood pressure of the subject was recorded after 10 minutes of rest, with the cuff of the mercury sphygmomanometer applied to the right upper arm. The approximate systolic BP was obtained by palpation. Then the cuff was deflated and re-inflated to about 10mmHg above the approximate systolic BP.

Phases I and V Korotkoff's sounds were used as systolic and diastolic BP respectively. The subject finally stands up and the BP was recorded after 2 minutes.

If standing was followed by a reduction of systolic BP of at least 20mmHg and or diastolic BP of at least 10mmHg, orthostatic hypotension was said to be present.[12]

The values obtained in the procedure above were interpreted as follows;

	Normal	Borderline	Abnormal
1. Resting Heart rate;	<100bpm	-	≥100bpm
2. HRR to valsalva manoeuvre;	≥1.21	1.11-1.20	≤ 1.10
3. HRR to deep breathing;	≥15bpm	11-14bpm	≤ 10bpm
4. HRR to standing;	≥1.04	1.01-103	≤ 1.00
5. BP response to standing: Systolic BP	<20mmHg	-	≥2ommHg
or/and Diastolic BP	<10mmHg	-	≥10mmHg

Each normal test was scored 0, borderline scored 0.5 and abnormal test scored 1.The 5 test results sum up to a maximum of 5 points. A total score of =3 was considered evidence of autonomic dysfunction[14] and the severity was graded as below:

- Mild DAN= 3.0-3.5
- Moderate DAN= 4.0-4.5
- Severe DAN= 5.0

A thorough neurological examination was carried out in a quiet room to assess functions of the higher centres, cranial nerves, motor and sensory systems.
Peripheral neuropathy was defined by the presence of any of the following:

- Loss of ankle jerk
- Loss of light touch sensation
- Loss of vibration sense or
- Loss of proprioception[7]

Also retinopathy was assessed for using a Welch-Allyn® ophthalmoscope after pupillary dilatation with 1% phenylephrine.

Venous blood was collected using a 10ml syringe and used as follows for laboratory tests;

a. 5ml for serum creatinine assay using Jaffe's method and
b. 5ml for serum fasting lipid profile estimation using enzymatic method. Both were read using colorimetry.

Capillary blood was collected through finger prick for fasting blood glucose estimation using Accu-Chek® advantage glucometer. FBS values of 110mg/dl and above were regarded as poor control.

Clean catch mid-stream urine was collected for albuminuria using dipstick method.

Flow chart showing the sequence of assessment of Cardiac autonomic function

1) Resting heart rate → 2) HRR to Valsalva manoeuvre → 3) HRR to deep breathing
↓
5) BP response standing ← 4) HRR to standing

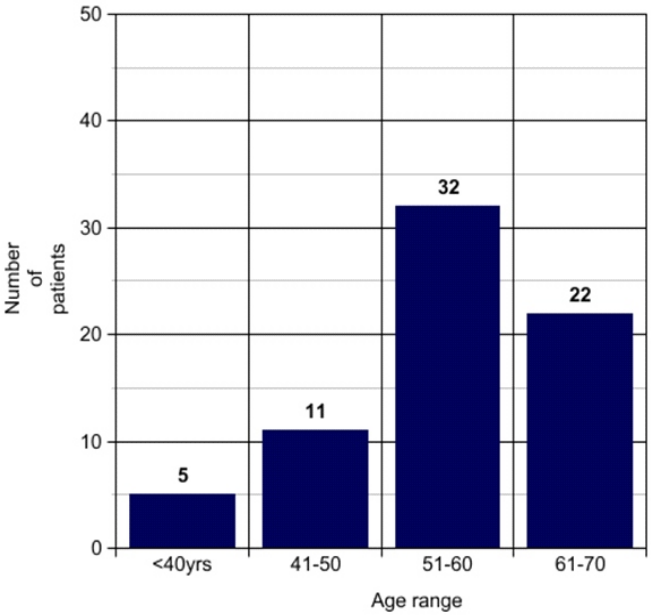
DATA ANALYSIS

The data were analysed using Statistical Package for Social Sciences (SPSS) version 19 software. Qualitative data were described as proportions and percentages while quantitative data were reported as mean and standard deviations. Student t-test was used to compare means while Odds ratio was used in assessment of associations between CAN and the variables. A p- value <0.05 was considered statistically significant. Sensitivity, specificity and positive predictive values for CAN were calculated for the five cardiac autonomic function tests.

RESULTS

A total of 150 type 2 DM patients were screened for the study. Seventy (70) of them were studied, having met inclusion criteria. This was made up of 27 (38.6%) males and 43 (61.4%) females. The mean age of patients was 55.76±8.62years. The age distribution of patients is shown in figure 1.

Figure 1: Age distribution



The mean duration of DM amongst the patients was 7.67yrs (SD=7.87yrs). Fifty three patients (76%) had had DM between 0 and 10yrs while 17 (24%) for > 10years.

The most common symptom of DAN noted in the patients was abnormal sweating pattern (37.1%) while the least was nocturnal diarrhoea (10%). The details are shown in table 1.

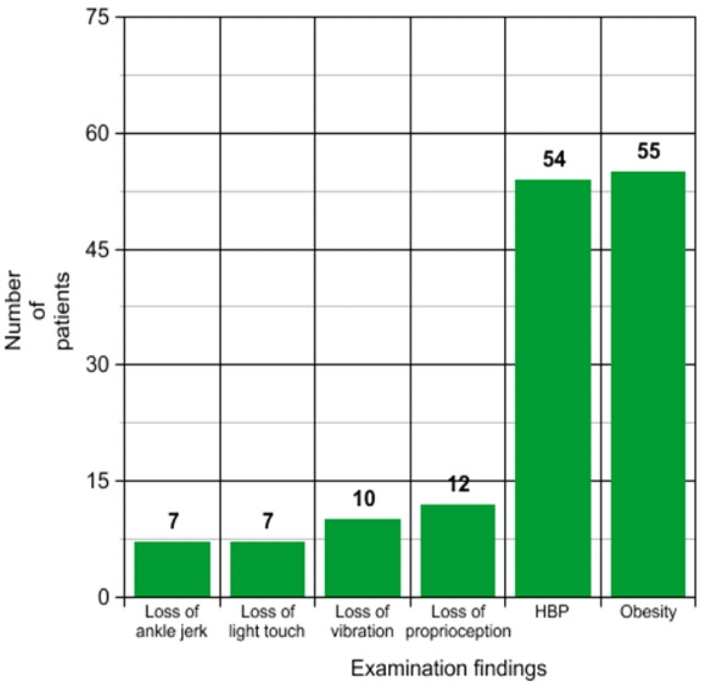
Table 1: Symptoms of autonomic dysfunction in patients

Symptoms of DAN	Patients (N=70) n(%)
Abnormal sweating pattern	26(37.1)
Erectile dysfunction (N=27)	20(74.1)
Postural dizziness	18(25.7)
Constipation	13(18.3)
Frequent diarrhoea	7(10.0)

Systemic hypertension and obesity were present in 54 (77.1%) and 55 (78.3%) of the patients respectively. Obesity was defined as waist circumference of > 102cm in males and >88cm in females.[15] Sixty-eight patient (97.1%) were right handed while 2 (2.9%) were left handed.

Peripheral neuropathy was present in 14 (18.6%) patients with type 2 DM. The details of examination findings are shown in figure 2.

Figure 2: Examination findings



The frequency of CAN in type 2 DM patients was 31(44.3%) as defined by 3 or more abnormal cardiac autonomic function test.[14]

The frequency of CAN increased with increasing age. The age groups of =40years and 61- 70years had the lowest and the highest frequencies respectively. The details are shown in table 2

Table 2: The age distribution of CAN in type 2 DM patients

Age range (Years)	CAN present n(%)
d40 (N=5)	1(20)
41-50 (N=11)	3(27.3)
51-60 (N=32)	15(46.9)
61-70 (N=22)	12(54.5)

Fourteen (52%) of the male patients and 17 (39%) of the female patients had CAN respectively.

Abnormal HRR to valsalva manoeuvre was the most common (87.1%) abnormal autonomic function test observed amongst the patients while resting tachycardia (7.1%) was the least common.

The details of pattern of abnormal cardiac autonomic function test in type 2 DM patients are shown in table 3.

Table 3: The pattern of abnormal autonomic function test

Autonomic function test	Patients N(%)	CAN Present n(%)	Sensitivity (%)	Specificity (%)	PPV (%)
Abnormal HRR to Valsalva manoeuvre	61(87.1)	31(50.8)	100	23	51
Abnormal HRR to deep breathing	49(70.0)	29(59.2)	94	49	59
Abnormal HRR to standing	47(66.7)	28(58.3)	90	49	58
Postural hypotension	16(23.3)	16(61.5)	52	74	62
Resting tachycardia	5(7.1)	2(40)	6	92	40

PPV= Positive predictive value

Twenty two (71%) patients had mild CAN while 25.8% and 3.2% had moderate and severe CAN respectively.

There was statistically significant association between duration of DM, hypertension, postural dizziness, abnormal sweating, peripheral neuropathy, retinopathy and proteinuria with CAN in type 2 DM patients. The details are shown in tables 4, 5 and 6.

Table 4: Association of demographic factors and level of DM control with CAN

Variables	CAN Present N(%)	CAN Absent N(%)	OR(95% CI)	df	p-value
Age(years)					
<60	20(44.4)	25(55.6)	1.02(0.38- 2.73)	1	>0.05
e60	11(44.0)	14(56.0)			
Sex					
Male	15(55.6)	12(44.4)	2.12(0.79- 5.62)	1	>0.05
Female	16(37.2)	27(62.8)			
Duration of DM					
1-10years	22(41.5)	31(58.5)	0.63(0.21- 1.89)	1	>0.05
>10years	9(52.9)	8(47.1)			
Frequency of blood glucose measurement					
Daily-weekly	12(36.4)	21(63.6)	0.54(0.21- 1.41)	1	>0.05
>weekly	19(51.4)	18(48.6)			
FBG level(mg/dl)					
<110	9(64.3)	5(35.7)	2.78(0.82- 9.40)	1	>0.05
e110	22(39.2)	34(60.8)			

Table 5: Association of symptoms of DAN with CAN

Variables	CAN Present N(%)	CAN Absent N(%)	OR(95%CI)	df	p-value
Postural dizziness	13(72.2)	5(27.8)	4.91(1.51-15.97)	1	<0.05
Abnormal sweating	18(69.2)	8(30.8)	5.37(1.87-15.41)	1	<0.05
Erectile dysfunction	12(60.0)	8(40.0)	3.80(0.58-24.28)	1	>0.05
Nocturnal Diarrhoea	5(71.4)	2(28.6)	3.56(0.64-19.77)	1	>0.05
Constipation	4(30.8)	9(69.2)	0.49(0.49-1.79)	1	>0.05

Table 6: Association of co-morbidities with CAN

Variables	CAN Present N(%)	CAN Absent N(%)	OR(95%CI)	df	p-value
Hypertension	28(50.9)	27(49.1)	4.14(1.05-16.34)	1	<0.05
Obesity	27(49.1)	28(50.9)	2.65(0.75-9.35)	1	>0.05
Retinopathy	18(72.0)	7(28.0)	6.33(2.14-18.74)	1	<0.05
Dyslipidaemia	12(50.0)	12(50.0)	1.42(0.53-3.83)	1	>0.05
Proteinuria	14(74.0)	5(26.0)	5.60(1.73-18.14)	1	<0.05

DISCUSSION

The study was carried out to determine the frequency and pattern of CAN in type 2 DM patients. The male to female ratio of 0.65 reported in this study is not in agreement with other hospital based studies. Ofoegbu[7] and Odusan[9] reported a sex ratio of 1.02. The difference could be from different sampling techniques applied in the studies. The former used stratified sampling technique while the latter used systematic sampling technique. The more preponderance of females in this study may suggest better health seeking behaviour of our female patients considering equal sex distribution of type 2 DM.[1]

The mean age of 55.76±8.62years reported in this study is nearly in agreement with the report of Odusan[9] which was 61.73±9.78years. It is not in agreement with the report of Ofoegbu[7] which was 46.29±11.30years. The difference with the latter could be from increasing longevity of DM patients due to improved medical care bearing in mind that the study was carried out about two decades ago. Also Ofoegbu[7] studied both type 1 and type 2 DM patients which can explain the lower mean age considering earlier onset of type 1 DM.

The frequency of type 2 diabetic CAN in this study was 44.3% and it is in agreement with other hospital based studies that reported frequencies ranging from 17-50%.[7] Ziegler et al[6] reported 34.3% in England, Odusan et al[9] reported 34.2% in Sagamu, and Anyiam 36.7% in Zaria.[16] In Enugu, Nigeria, Ofoegbu[7] and Ukpabi[8] reported 12.4% in 1992 and 29% in 2001 respectively while this study reported 44.3% still in Enugu. Above suggests increasing frequency of CAN which could be from improved DM care with consequent increased longevity. This is supported by the mean age of the diabetic patients as reported in this study which is 11years more than the report of Ofoegbu[7] in 1992. Also, Ofoegbu defined CAN by the presence of an abnormal Valsalva maneuovre.

The frequencies of CAN in male and female patients were 52% and 39% respectively. This is in agreement with the report of Odusan et al.[9] The above could be from a higher tendency for male patients to have other risk factors for CAN other than DM like alcohol use.

The symptoms of DAN observed in this study include abnormal sweating pattern, erectile dysfunction (ED), postural dizziness, nocturnal diarrhoea and constipation in descending frequency.

Abnormal sweating pattern and postural dizziness showed significant statistical association with type 2 diabetic CAN while erectile dysfunction, nocturnal diarrhoea and constipation did not show significant statistical association with type 2 diabetic CAN. These findings are in agreement with the findings of Abbasher et al in Sudan.[17] The absence of association between nocturnal diarrhoea and type 2 diabetic CAN could be as a result of other aetiologies of diarrhoea like infections and drugs side effects of anti-diabetic drugs.[4]

Erectile dysfunction (ED) was noted in 74.1% of males in this study and it is higher than 7% reported by Abbasher et al.[17] This difference could be that the former reported for males while the later reported for total sample with women inclusive. Also sexual history is sensitive and could cause embarrassment amongst patients. This could make interviewers reluctant in getting proper sexual history.[18] Furthermore, multifactorial pathogenesis of ED could have contributed in its high frequency. The absence of significant association between ED and CAN could have resulted from other aetiologies of ED like use of anti-hypertensive drugs, vascular disease, metabolic factors, malnutrition, endocrine disorders, psychogenic factors, and use of anti-diabetic drugs.

This study showed significant association of hypertension with diabetic CAN. This is in agreement with the report of Odusan et al[9], Ling et al[19] and Witte et al.[20]

This could result from the fact that both type 2 DM and hypertension are component in the spectrum of insulin resistance syndrome. Also, there are other mechanisms of hypertension in type 2 DM like fluid and salt retention effects of insulin, increased sympathetic nervous system activity, reno-vascular hypertension through accelerated atherosclerosis and DM nephropathy.[21]

The frequency of somatic peripheral neuropathy in this study was 18.6%. It had significant statistical association with diabetic CAN. This is due to the fact that both are neuropathies and they have common aetiology which is from chronic hyperglycaemia.[22-33] This is in agreement with the report of Ofoegbu[7], Ugoya et al[10], Ling et al[19], Witte et al[20], and Pappachan et al.[34]

The frequency of type 2 diabetic CAN progressively increased with increasing age of the patients in this study. Those with age <40years had the frequency of 20% while those between 61 and 70years had 54.5%. This is in agreement with the findings of other hospital based studies. Ofoegbu[7] reported a significant statistical association between diabetic CAN and increasing age. This association could be derived from the fact that older patients would have had DM for longer duration and also old age is a risk factor for CAN in the absence of DM due to ageing itself and other co-morbidities.

This study revealed that 87% of the type 2 diabetic patients had abnormal HRR to Valsalva manoeuvre and it is the most sensitive (100%) test for assessing CAN. This is in agreement with the report of Pappachan et al[34], though they reported 45% prevalence. The above difference could be attributable to the shorter mean duration of DM and younger mean age of their sample population.

Furthermore, resting tachycardia was the least observed test of CAN in this study and it was the most specific test. It was in agreement with the report of Pappachan et al[34] but not in agreement with Gelber et al[35] who reported HRR to deep breathing as the most specific test (80%) and best positive predictive value. Also, Gelber et al[35] noted that HRR to deep breathing was most widely used test of cardiovagal function.

Postural hypotension and resting tachycardia had the best (62%) and least (40%) positive predictive values for CAN.

Seventy-one percent (71%) of the patients with diabetic CAN had mild form. This is in agreement with the report of Abbasher et al in Sudan.[17] Above result could be due to some exclusion criteria like CKD which ruled out patients with advanced CAN. Also, it could suggest improved care for DM patients with mild to moderate complications. Most of the studies in Nigeria did not grade the severity of diabetic CAN.

CONCLUSION

The frequency of CAN is high (43.1%) amongst type 2 DM patients in UNTH Enugu and postural hypotension had the best positive predictive value for the diagnosis of CAN in the study population.

Also, the frequency of erectile dysfunction is very high (74%) amongst male type 2 diabetic patients.

Furthermore, the presence of postural dizziness, abnormal sweating pattern, hypertension, peripheral neuropathy, proteinuria and retinopathy had significant statistical association with CAN in the study population.

Finally, most of the type 2 diabetic patients had poor glycaemic control.

RECOMMENDATIONS

Autonomic dysfunction is a prevalent and serious complication for individuals with type 2 diabetes mellitus. The clinical manifestations of autonomic dysfunction can affect daily activities (e.g., exercise), produce troubling symptoms (e.g., syncope), and cause lethal outcomes. The patient's history and physical examination are ineffective for early detection of autonomic nerve dysfunction, and thus recommendations for the use of non-invasive tests that have demonstrated efficacy are warranted.

Given the clinical and economic impact of this complication, testing of diabetic individuals for cardiovascular autonomic dysfunction should be part of their standard of care.

Poor glycaemic control was one of the identified risk factors for type 2 diabetic CAN and most of the patients had poor glycaemic control. It is recommended that doctors should be more aggressive in blood glucose control in order to forestall the morbidity and mortality of this condition.

Considering the high frequency of erectile dysfunction amongst male type 2 diabetic patients, it is recommended that proper sexual history be part of their standard care.

If only one index of measurement of CAN is to be used in any study, it is recommended that postural hypotension be applied due to its best positive predictive value.

It is recommended that further multi-center integrated studies be carried out on a larger population of type 2 DM patients in different parts of the country to get the true current prevalence.

LIMITATIONS OF THE STUDY

1. This study, being cross sectional, could not establish strong associations as longitudinal studies.
2. A more reliable assessment of blood glucose control which is Glycated haemoglobin (HbA_{1C}) assay was not done due to its unavailability in our facility as at the time of this study.

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