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Research Article

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# Frequency and Risk Factors of Cardiac Autonomic Neuropathy in Patients with Diabetes Mellitus Tripoli- Libya (2018)

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## ABSTRACT

Cardiac autonomic neuropathy (CAN) is a frequent chronic complication of diabetes mellitus (DM) with potentially life-threatening outcomes, although there are available simple bedside tests for diagnosis, it is often overlooked.

The study aimed to determine frequency and risk factors of CAN in patients with DM attended diabetes out-patients clinic at Tripoli diabetic hospital.

A descriptive prospective study include one hundred diabetic patients attended diabetes out-patients clinic from October 2017 till April 2018, were assessed by the autonomic function tests. CAN was assessed by analyzing heart rate (HR) variations during resting and deep breathing. Sympathetic functions were assessed by checking orthostatic hypotension. ECG (in deep breathing) was done. Trans-thoracic echocardiography, stressing on left ventricular hyper trophy (LVH), and systolic functions were carried out. Data analysis was done by SPSS program version 16.

A total of 100 patients included in the study, female were 53%, mean age was 51.96±1.46, CAN was detected in 63% of studied cases, diabetics with CAN were significantly associated with longer duration of DM (*P*-value = 0.016), un-controlled hypertension (*P*- value =0.004) , high fasting lipid profile (*P* -value =0.005), and presence of other diabetes microangiopathy (*P*-value =0.003)**.**

CAN was more common with prolonged duration of DM, uncontrolled hypertension, dyslipidemia and presence of other micro-vascular complication of DM

Identification of CAN is crucial because it can lead to severe morbidity and mortality and increase risk of sudden cardiac death.

***Keywords-*** *Cardiac; Autonomic Neuropathay; Diabetes Mellitus; Risk factors; Tripoli.*

## INTRODUCTION

Diabetes mellitus (DM) is a global health epidemic. Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in patients with DM.[1,2] Cardiac autonomic neuropathy (CAN) is a common under-diagnosed complication of DM.[3] The impact of CAN on patients with DM can be distressing, with CAN revealed to be related with increased mortality, CVD, chronic kidney disease (CKD), and morbidity of DM[4] CAN has several risk factors that are common to other diabetes-related vascular complications, such as diabetes duration, poor glycemic control, and CVD risk factors, including obesity, smoking, hypertension, hyperlipidemia and presence of other micro-vascular complications, have all been associated with CAN development.[5,6]

Based on the CAN subcommittee of the Toronto Consensus Panel on Diabetic Neuropathy[7] and the American Diabetes Association (ADA)[8], CAN is defined as the impairment of cardiovascular autonomic control in patients with DM following the exclusion of other causes. Cardiovascular autonomic reflex tests (CARTs) are usually used for CAN diagnosis and staging.[7]

For Ewing test, Valsalva index, E/I and 30s/50s mainly represent the parasympathetic functions, while the difference between blood pressure responses to standing and supine position can assess the sympathetic functions.[7,8]

The aim of this study was to determine prevalence and risk factors of CAN in Libyan patients with DM attending diabetic clinic from October 2017 to April 2018.

## MATERIALS AND METHODS

A descriptive prospective study included 100 patients with DM, attended diabetes out-patients clinic from October 2017 to April 2018 at Tripoli diabetic hospital. Type of DM classified into type 1, type 2 DM based on clinical assessment (Auto-antibodies not available). A special performa was completed for every patient after verbal consent taken, which included details on gender, body mass index (BMI), age, duration of diabetes, history of smoking, mode of anti-hyperglycemic treatment, history of dyslipidemia, any micro-vascular complication of DM and investigation results of HBA1C, low density of lipoprotein (LDL), high density lipoprotein( HDL), Triglycerides (TGA), were included.

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Clinical examination, with stress on heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure were undertaken. Testing of autonomic parasympathetic dysfunction was assessed by HRV testing of Ewing's methodology 1980[7,8] (heart rate ECG RR intervals on resting, and deep respiration). Heart rate variability was calculated from the RR interval using short continuous ECG recording. Heart rate response to the Valsalva maneuver was omitted from testing in our patients because it can induce Valsalva retinopathy.[9]

Testing for sympathetic dysfunction by postural hypotension in supine and after standing for 3 min was undertaken with the standard mercury sphygmomanometer. The measurement in the supine position was taken after at least 15 min of rest and measurement in standing position was taken at the third minute of standing. Trans-thoracic echocardiography (vivid7GE) used for assessing systolic function of the patients, detecting ischemic changes and measuring the left ventricular thickening (inter-ventricular septum, posterior wall), the echocardiography protocol based on the recommendation and guidelines of the American Society of Echocardiography.[10]

The frequency and the risk factors of CAN were assessed according to the autonomic function tests of Ewing's methodology.

***Exclusion criteria*:**

Systemic illness that can affect the study results or the autonomic functions as congestive heart failure (CHF), coronary artery disease (CAD), arrhythmia, thyroid dysfunction, concomitant treatment with adrenergic antagonists that can affect the results of autonomic function tests, were excluded.

***Statistical analysis*:**

Analysis was performed by using the statistical package for social science program (SPSS) version 16. The data were presented as frequency and percentages, with application of Chi square tests and significance was considered when *P* value was less than 0.05.

## RESULTS

In present study, 100 patients with DM were included, 53% of them were female, their age ranged from 20 to 70years (mean 51.96 ± 1.46years), 79% were from Tripoli, and 54% were employers. Non -smokers were 70% (Table 1).

Type 2 DM were presented in 84% of cases, 29% were on oral hypoglycemic agents, 27% of cases were under combined insulin and OHD, and 44% were on insulin only. There was 15% newly diagnosed (< 1 year), and about 42% of them were more than 10 years. BMI were normal (18.5-24.5%) in 34% of cases, 43% were overweight (BMI=25-29.5%), 17% were obese (BMI=30-39.5%), and 6% with morbid obesity (BMI≥40%). Blood pressure was measured for every patients after 15min rest, controlled (≤130/80 (either not hypertensive or controlled with treatment) in 32% of cases (Table 2).

Their HBA1c was on target only (<7%) among 10% of cases, diabetic micro-vascular complications were present in 54% of cases. Normal lipid profile was normal in 18% of cases (Table 3).

The frequency of CAN as assessed by Ewing's tests, signs of autonomic neuropathy including HRV tests E/I ratio (expiration to inspiration) standing to lying flat, was 63%. Diabetics with CAN were significantly associated with longer duration of DM (*P*-value =0.016), un-controlled hypertension (*P*- value=0.004), high fasting lipid profile (*P*-value =0.005), and presence of other diabetes micro-angio-pathy (*P*-value =0.003) (Table 4).

**Table 1:** Socio- demographic characteristics of patients at Tripoli Diabetes Hospital, 2018**.**

| Character | No (%) |
|---|---|
| ***Sex:*** | |
| Female | 53 (53%) |
| Male | 47 (47%) |
| ***Age in years*** | |
| ≤30 years | 9 (9%) |
| 31-50 | ٣7 (37%) |
| 51-65 | 40 (40%) |
| >65 | 14 (14%) |
| ***Address*** | |
| Tripoli | 79(78%) |
| Outside Tripoli | 21(22%) |
| ***Occupation*** | |
| Employer | 54(54%) |
| Non | 46(46%) |
| ***Smoking*** | |
| Non-smoker | 70(70%) |
| Active smoker | 19(19%) |
| Passive Smoker | 4(4%) |
| Ex- smoker | 7(7%) |

**Table 2:** Clinical characteristics of patients at Tripoli Diabetes Hospital, 2018.

| Character | No. (%) |
|---|---|
| ***BMI*** | |
| Normal | 34 (34%) |
| Overweight | 43 (43%) |
| Obese | 18 (18%) |
| Morbid obesity | 5 (5%) |
| ***Type of DM*** | |
| Type1 | 15 (15%) |
| Type2 | 85 (85%) |
| ***Duration of DM*** | |
| **≤ 1year** | 15 (15%) |
| **2-9 years** | 43 (43%) |
| **≥ 10 years** | 42(42%) |
| ***Hypertension*** | |
| Controlled | 32(32%) |
| Un-controlled | 68 (68%) |
| ***Treatment*** | |
| Oral hypoglycemic drugs | 29(29%) |
| Combined | 27(27%) |
| Insulin | 44(44%) |
| **Diabetes micro-angiopathy** | |
| **Presence** | 58(58%) |
| **Absent** | 42(42%) |

**Table 3:** Chemical profile of patient's character at Tripoli Diabetes Hospital, 2018.

| Investigation | No. (%) |
|---|---|
| ***HbA1c*** | |
| 7-٦,٥% | 10(10%) |
| >7-8% | 32(32%) |
| >8% | 38(38%) |
| Unknown | 20(20%) |
| ***Fasting lipid profile*** | |
| Normal | 18(18%) |
| Abnormal | 49(49%) |
| On treatment | 18(18%) |
| Unknown | 15(15%) |

**Table 4**: Distribution of the patients character according to Ewing's tests for CAN diagnosis at Tripoli Diabetes Hospital, 2018.

| Factor | Absent CAN | Present CAN | *P* value |
|---|---|---|---|
| ***Sex :*** | | | |
| Female | 23 | 30 | 0.102 |
| Male | 14 | 33 | |
| ***Age:*** | | | |
| ≤30 years | 2 | 7 | 0.452 |
| 31-50 | 12 | 25 | |
| 51-65 | 15 | 25 | |
| ≥65 | 8 | 6 | |
| ***Smoking:*** | | | |
| Non | 30 | 40 | 0.531 |
| Active | 5 | 14 | |
| Passive | 1 | 3 | |
| Ex | 1 | 6 | |
| ***Duration*** | | | |
| ≤1 year | 9 | 6 | 0.016 |
| 2-9 | 18 | 25 | |
| ≥10 | 10 | 32 | |
| ***BMI:*** | | | |
| Normal | 11 | 23 | 0.337 |
| Overweight | 15 | 28 | |
| Obese | 8 | 10 | |
| Morbid obesity | 3 | 2 | |
| ***Hypertension*** | | | |
| Controlled | 18 | | 0.004 |
| Un-controlled | 19 | 14 | |
| | | 49 | |
| ***HBA1c*** | | | |
| 7-٦,٥% | 5 | 5 | 0.582 |
| >7-8% | 11 | 21 | |
| >8% | 12 | 26 | |
| ***Fasting Lipid Profile*** | | | 0.005 |
| Normal | 12 | 6 | |
| Abnormal | 12 | 37 | |
| On treatment | 7 | 11 | |
| **Type of DM** | 2 | 13 | |
| Type1Type2 | 35 | 50 | 0.120 |
| ***Diabetes Micro-angiopathy*** | | | 0.003 |
| Present | 12 | 3 | |
| Absent | 25 | 60 | |

## DISCUSSION

It was aimed in the present study to determine the frequency and identify risk factors of CAN in patients with DM who attended diabetes out-patient clinic at Tripoli diabetes hospital.

The prevalence of CAN in the present study was (63%), in comparison with other studies, it was ranged from as low as 2.5% (DCCT)[11] to as high as 90% in long standing DM and in 69% of treatment induced neuropathy.[11] The prevalence of Cardiac autonomic Neuropathy CAN vary depended on patients anticipated, the investigative technique used and disease stage.[12,13]

In lamer et al study, cardiac autonomic neuropathy was present in (37.0%)[14], while in Mendivil et al study was 68%[15] and It was higher than that of Zeigler et al[16] 34.3% .

There was a strong association with presence of CAN and prolonged diabetes duration (*P*-value =0.016 , in newly diagnosed (< 1 year ) CAN was present in (6 out of 9=40%) 6%, but after 10 years it was 32% (32 out of 42 =76%) .

The duration of DM is an independent factor for emergent CAN irrespective of diabetes type.[16] CAN is discovered in about 7% of patients with DM type 1 or 2 at presentation, and it is expected that the risk rises annually by about 6% and 2% in patients with DM type 1 and 2, respectively.[17] The prevalence of CAN increased from 9% at the close of the DCCT study to 31% 1 year afterward, Uncontrolled DM is a major risk for CAN progression. In the Diabetes Control and Complication Trial (DCCT), intensive blood sugar control resulted in 50% drop in CAN rate over the 6.5 years, other trials directing hypertension, smoking, obesity, and dys-lipidemia furthermore reduced the rate of CAN. The effect of sex on CAN is controversial.[6]

Also, the frequency of CAN increased from 19.8% in patients with pre-diabetes to 32.2% in patients newly diagnosed with T2DM,[18] with higher prevalence reported in patients with T2DM and longer diabetes duration.[16] The rate of CAN is frequently described to be greater in T2DM compared to T1DM, in spite of the longer diabetes duration in patients with T1DM; probably an indication of patients with T2DM frequently being older and more prone to have additional CVD risk factors for CAN than patients with T1DM. The EURODIAB IDDM complications study did not show differences in CAN rate between male (35%) and female (37%)[19] similar to present study. In present study the number of patients with CAN in controlled blood pressure group (either not hypertensive or controlled with treatment) were 14% (14 out of 32=43%),where as it was 49% (49 out of 68=72%) in uncontrolled blood pressure group, presence of CAN had a significant association with uncontrolled blood pressure (*P* value =0.004). A cross-sectional study of 2,230 participants with T2DM also showed that CAN patients had a higher prevalence of hypertension *vs* patients without CAN.[20]

The present study showed insignificant association between presence of CAN and Body Mass Index, but in other studies showed that CAN was independently

associated with obesity (*P*=0.034) and that specifically in T2DM there was higher prevalence of CAN in obese patients (*P*=0.033).[21] Other study suggested that central obesity was associated with CAN, along with age, postprandial glycemia, and diastolic blood pressure (DBP).[18]

Kodama et al.,[22] in a meta-analysis study described the association of pulse pressure as a cardiovascular risk in DM. Makimattila et al.[23] found that poor glycemic control was the most important independent predictor of decrease in all measures of absolute power of HRV.

In present study the number of cases with CAN is increased at higher HBA1c (7% i.e. 5 out of 63, when HBA1c was ≤ 7g% versus 41% 26 out of 63 at HBA1c ≥ 8g%. Dyslipidemia (high LDL-cholesterol± increased TGA) shown a significant association (*P* value=0.005) ).

The current study showed that, there was a significant association between presence of both CAN and other micro-vascular complication (*P* value was 0.003), the number of patients with both complications was 3% (3 out of 15 =20%), whereas the number of patients with CAN and no micro-vascular complication were 60% (60 out of 85=70%). Similar results were found in the EURODIAB,[12] study that the presence of retinopathy and albuminuria was associated with CAN. Current findings are in agreement with those of Voulgari et al.[24] who mentioned that in type 2 DM patients, CAN has been independently associated with elevated BP, hyperglycemia, longer diabetes duration, dyslipidemia and the presence of microvascular complications.

## CONCLUSIONS

CAN is a frequent chronic complication of DM with potentially life-threatening outcomes. Although there are available simple bedside tests for diagnosis of CAN, it is often overlooked. CAN was more common with prolonged duration of DM, uncontrolled hypertension, dyslipidemia and presence of other micro-vascular complication of DM.

## RECOMMENDATIONS

Screening for CAN should be performed at the diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes, particularly in patients at greater risk of CAN due to a history of poor glycemic control, cardiovascular risk factors, DPN, and macro- and micro-angiopathic diabetic complications.Intensive diabetes therapy, intensive multi-factorial cardiovascular risk reduction and lifestyle intervention are recommended in patients with CAN.

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