Screening and assessment of cardiac autonomic neuropathy in long-standing type 2 diabetic women

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Background
Patients with long-standing diabetes mellitus undergoing surgical interventions are under considerable risk, hence posing a surgical challenge, as they may have cardiovascular and/or cardiac autonomic neuropathy (CAN). CAN is serious, often overlooked and underdiagnosed, with possible arrhythmias and silent ischemia that may be life threatening.

Objectives
The aim of this study was to screen for one of the underdiagnosed high-risk problems by assessment of CAN in long-standing type 2 diabetic women undergoing stressful situations.

Study design
Cross-sectional study.

Patients and methods
Hundred type 2 diabetic women scheduled for major surgery were assessed by autonomic function tests. CAN was assessed by analyzing heart rate variations during three standard tests (deep breathing, lying to standing, and the valsalva maneuver). Sympathetic functions were assessed by checking orthostatic hypotension. The CAN score of each patient was analyzed. Continuous 24 h ECG monitoring was performed to evaluate arrhythmia, corrected QT (QTc), and QT dispersion (QTd). Transthoracic Doppler echocardiography, with a focus on left ventricular hypertrophy, diastolic, and systolic dysfunctions, was carried out. Patients were classified as having mild (with only one abnormal test) or severe CAN when two or more abnormal function tests were present. Exclusion criteria included any systemic illness that could affect the results of the study or the autonomic functions, smoking, hypertension, and patients with evident ischemia.

Results
CAN was detected in 70% of the patients studied, and 70% of them had a severe case of CAN. Postural hypotension was detected in 34% of the patients studied. QTc prolongation and QTd were frequent. ECG and Doppler echocardiography changes of left ventricular hypertrophy were more prevalent among patients with CAN. Diabetics with CAN were significantly older, had a longer duration of diabetes mellitus, and higher HbA1-c, higher pulse pressure, triglyceride, uric acid, and urinary albumin excretion rate. They also had a significantly increased left ventricular mass index and diastolic dysfunction.

Conclusion
Middle-aged women with long-standing diabetes are vulnerable to CAN with postural hypotension and prolonged QTc intervals, QTd, and increased left ventricular mass index. Identification of CAN is crucial to prevent the hazards of cardiovascular insults during stressful situations, and cases with severe CAN may require coronary artery disease screening preoperatively.

Keywords:
cardiac autonomic neuropathy, coronary artery disease, diabetes

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Introduction

Autonomic neuropathy, although not rare, is one of the most insidious complications of diabetes mellitus (DM), especially if long standing and poorly controlled. Cardiac autonomic neuropathy (CAN) is often overlooked both in the diagnosis and the treatment simply because there is no widely accepted single approach to its diagnosis [1]. CAN involves exercise intolerance, intraoperative cardiovascular (CV) liability, orthostatic syndromes, and silent myocardial ischemia [2–4]. These clinical manifestations can result in life-threatening outcomes that unquestionably associate the presence of CAN with the increased risk of CV morbidity and mortality in DM.

In the Eurodiab prospective study (2001), CAN was among the strongest risk markers of future total and CV mortality exceeding the effect of traditional risk factors

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such as age, obesity, hypertension, dyslipidemia, inflammatory, and prothrombotic emerging cardiac risk factor [4,5]. In a meta-analysis of 12 published studies, Vinik *et al.* [6] reported a constant association between CAN and silent myocardial ischemia and in the DIAD study, CAN was a stronger predictor of silent ischemia and subsequent cardiac events [7].

The corrected QT (QTc) interval and QT dispersion (QTd) have been considered as markers of cardiac autonomic dysfunction and have been shown to be independent predictors of CV mortality and all-cause mortality risk in patients with type 2 DM [4]. Combined abnormality in heart rate variability (HRV) and the QT index was a strong predictor of mortality independent of conventional risk factors [8,9].

Action to Control Cardiovascular Risk in Diabetes (ACCORD trial 2010) in the presence of CAN at baseline was an independent contributor to the higher CV mortality risk in both the intensive and the standard glycemic arm treatment. Individuals with baseline CAN were two times more likely to die compared with individuals without CAN [10,11]. Considerable attention has been paid to the CV aspect of autonomic dysfunction, especially with the view regarding the association of very tight glycemic control with increased mortality. The ACCORD trial [12] attributed increased mortality to hypoglycemia-induced arrhythmias [1].

There is no widely accepted single approach to the diagnosis of CAN; however, during the 1970s, Ewing *et al.* [13] recommended a number of simple bedside tests of short-term RR difference (the distance between 2 successive ventricular contractions on ECG recording) to detect CAN including changes in RR with deep breathing, RR response to standing that induce reflex tachycardia, followed by bradycardia and Valsalva ratio, which evaluates the cardiovagal function in response to a standard increase in intrathoracic pressure.

Orthostatic hypotension, with its many troublesome symptoms ranging from light headedness to near syncope, which may be associated with poor quality of life with a decrease in systolic blood pressure (SBP) of at least 20 mmHg and of at least 10 mmHg in diastolic blood pressure (DBP) during 3 min of standing and resolving with sitting or lying down, is characteristic of CAN [14,15].

The clinical symptoms of CAN may be late; however, subclinical CAN manifest as changes in HRV may be detected within 1 year of diagnosis of type 2 DM [16].

Pop-Busui *et al.* [17] reported that screening for CAN showed that it ranges from as low as 2.5% (Diabetes Control Complications Trial, 1974) to as high as 90% in long-standing DM and should be instituted at diagnosis of type 2 DM and after 5 years of diagnosis of type 1 [18]. Vinik and Ziegler [19] reported that detection of CAN is a must before exposing patients with long-standing DM to stressful situations and also before planning exercise. Diabetics must be tested with a cardiac stress test before undergoing an exercise program. Patients with CAN need to rely on their perceived exertion and not heart rate to avoid the hazardous levels of exercise intensity [19].

Aims

This study aimed at screening and assessment of cardiac autonomic dysfunction in middle-aged women with long-standing type 2 DM who would be exposed to stress in the form of major surgery.

Design

Cross-sectional study.

Patients and methods

The patients studied included 106 women who were known to be diabetic and were on oral hypoglycemic agents (70 cases) and 36 cases who were on combined insulin and sulfonylurea. All were receiving metformin 1.7 g/day. Six patients did not complete the study for unknown reasons and only 100 patients completed the study. Their ages ranged from 40 to 60 years (mean 52.4 ± 3.7 years). The patients studied had no polyps symptoms. The mean duration of DM was 10 ± 2 years, ranging from 6 to 14 years. BMI ranged from 25.1 to 29.2 (mean 27.1 ± 1.1).

All medications that could affect the results of the study or the autonomic functions were withhold during and 1 week preceding the clinical assessment of autonomic functions.

Examinations were performed in the morning at least 2 h after a light breakfast and no caffeine was allowed. The patients were asked about symptoms suggestive of autonomic neuropathy, postural hypotension, and myocardial ischemia.

Diabetic complications such as retinopathy were checked, with a focus on peripheral neuropathy and sudomotor neuropathy. Peripheral neuropathy and sudomotor neuropathy were detected clinically by monofilament and dryness of the feet. Clinical examination, especially heart rate, SBP, DBP, and pulse pressure, was performed. Autonomic parasympathetic dysfunction was assessed by HRV testing (heart rate, ECG, and RR intervals on resting, standing, respiration, and valsalva). HRV was calculated from the RR interval using short continuous ECG recording. Continuous 24-h ECG monitoring (Schiller/MT101, Holter, Switzerland) was also used to evaluate ischemia, arrhythmia, QTc intervals, and QTd. Cases with evident ischemia or arrhythmias were not included. The resting 12-lead ECG was also performed to determine beside HRV evidences of left ventricular hypertrophy (LVH) and/or ischemia. Prolongation of the QTc interval greater than 460 ms and QTd greater than 10 ms were considered as evidences of HRV. Flattening of the T wave and ST segment depression were considered as evidences of myocardial ischemia. Cases with angina ECG and Holter monitor evidences of ischemia were not included in the screening study.

Testing for sympathetic dysfunction by postural hypotension in a supine position and after standing for 3 min was carried out using the standard mercury sphygmomanometer. The measurement in the supine position was taken after at least 15 min of rest and the measurement in the standing position was taken in the third minute of standing.

Transthoracic Doppler echocardiography was performed, with a focus on left ventricular mass index, diastolic, and systolic dysfunctions.

Biochemical studies were carried out, with a focus on blood glucose, fasting, and post 75 g glucose challenge together with HbA1-c, serum creatinine, plasma cholesterol, triglyceride, serum uric acid, and 24 h urine albumin excretion.

The prevalence and severity of CAN were assessed according to the number of autonomic function tests of Ewing's methodology, and the CAN score in each patient was analyzed.

Subclinical CAN cases or mild CAN with only one abnormal function test were compared with severe CAN cases (two or more abnormal autonomic functions).

The study protocol was approved by the scientific committee of the Mansoura Faculty of Medicine and informed consent was obtained.

Exclusion criteria

Patients with systemic illness that could affect the results of the study or autonomic functions such as congestive heart failure, coronary artery disease, arrhythmia, renal, hepatic impairment, hepatitis C virus infection, severe anemia, thyroid dysfunction, smoking, concomitant treatment with anticholinergic agents, adrenergic antagonists, vasoconstrictive agents, and patients with blood pressure (BP) of at least 140/90 mmHg on two occasions 2 weeks apart were not included.

Statistical analysis

Statistical analysis was carried out using the statistical package for social science program, version 16 (SPSS Inc., Chicago, Illinois, USA). The qualitative data were presented as frequency and percentages. The quantitative data were examined using the Kolmogorov–Smirnov test to test for normal distribution of the data and, when parametric, were expressed as mean and SD. The Student *t*-test was used to test for differences in normally distributed quantitative data between the two groups. The Mann–Whitney *U*-test was used for comparison between two groups when data were not normally distributed. A *P*-value less than 0.05 was considered significant.

Results

The prevalence of CAN as assessed by signs of autonomic neuropathy including HRV tests of the expiration to inspiration ratio (E/I) standing to lying flat and valsalva maneuver was 70% (20 cases with single HRV testing, 26 cases with three HRV testing, and 24 cases with moderate CAN where two HRV tests were present).

Postural hypotension was detected in 34% of the studied cases and the mean pulse pressure was significantly elevated in diabetics with CAN compared with those without CAN ($P<0.01$).

Prolonged QTc (>460 ms) was found in 42% of all the studied cases and 60% of the CAN cases, and significantly increased QTd (>10 ms) was observed in the CAN group compared with the non-CAN group as evident from continuous 24 h ECG Holter monitoring.

Women with DM and CAN were significantly older, with a significantly longer duration of uncontrolled DM with insignificant differences in BMI.

There was no significant difference in the prevalence of CAN in relation to the method of controlling hyperglycemia (oral vs. combined oral hypoglycemic and insulin).

Symptoms suggestive of CAN in other systems, mainly urogenital, were evident in the CAN group ($P<0.04$). Peripheral neuritis detected by monofilament with dryness of their feet ($P<0.01$). SBP, DBP, and the mean pulse pressure were significantly higher in the CAN group ($P<0.001$).

Transthoracic echo Doppler indicated the presence of mild LVH (LV wall mass index ≥ 126 g/m^2 in 70.01% of CAN vs. 33.3% in the non-CAN group, $P<0.001$) and a significant abnormal relaxation pattern (E/A<1) with preserved LV systolic functions.

Significantly higher BG level and HbA1-c were observed in the CAN group, with significant hypertriglyceridemia and elevation in uric acid in the CAN group. The urinary albumin excretion in the CAN was significantly elevated compared to that in the non-CAN group ($P<0.01$). Comparison of the studied parameters in relation to the severity of CAN showed insignificant changes apart from significantly older age, more postural hypotension, HbA1-c, serum creatinine, urine albumin excretion, and QTc. Signs of LVH and QTd indicated a borderline significant increase in severe CAN cases.

Discussion

The present screening study aimed to evaluate CAN in middle-aged women with long-standing diabetes who would be experiencing a stressful situation in the form of major surgery. Detection of CAN preoperatively is necessary as such patients are vulnerable to perioperative CV instability, with a greater decrease in heart rate and BP during induction of anesthesia and more severe hypothermia [3,19].

In the present study, the prevalence of CAN detected by the methods of Ewings *et al.* in the 1970s using HRV tests [13] was high (70%). As the determination of CAN is usually based on a battery of autonomic function tests and as the proceeding from a consensus conference

(1992) [20], recommended three tests. The three tests were: inspiration/expiration ratio, standing to lying flat, Valsalva's maneuver for parasympathetic. Postural hypotension for sympathetic. In the present study, the gold standard clinical autonomic testing [21] was followed (expiration/inspiration ratio, standing to lying flat, and valsalva maneuver, and postural hypotension) (Tables 1 and 2).

The prevalence of CAN ranged from 20 to 42% according to the method of detection of the HRV state, being the highest (30%) by the valsalva maneuver procedure and the lowest (20%) by the reduced E/I ratio and by standing to lying flat. The CAN score was calculated, where more than one-fourth (26%) had at least 3 positive tests and 24% had at least 2 positive. This is in agreement with the study of Katsilambros *et al.* [1], who found that autonomic neuropathy and CAN are not rare, but often overlooked.

The prevalence of CAN ranged from as low as 2.5% (DCCT) [17] to as high as 90% in long-standing DM and in 69% of patients with treatment-induced neuropathy [22]. In the present study, the valsalva ratio was 30% and the E/I ratio was 20%. Our results are not in agreement with England *et al.* [23], who found that HRV with deep breathing is the most widely used test of cardiovagal parasympathetic dysfunction. CV sympathetic function was assessed by measuring the BP response to orthostatic changes [24,25] and was detected in 34% of the studied cases (Table 3).

The prevalence of CAN in the present study is higher than that of Ziegler *et al.* [26], who, using HRV tests, found that 34.3% of type 2 DM patients had abnormal functions. Similar to Cabezas-Cerrato *et al.* [27], the HR response to deep breathing in the present study was the least evident among the studied cases.

In the present study, the patients studied were all women; this could avoid sex-related difference in biochemical and hematological values [28,29]. CAN was more prevalent in diabetics of longer duration, older age, those with more pulse pressure, higher serum triglycerides, and those with more elevated HbA1-c. Kodama *et al.* [30], in a meta-analysis study, described the association of pulse pressure as a CV risk in DM. Mäkimattila *et al.* [31] found that poor glycemic control was the most important independent predictor of a decrease in all measures of absolute power of HRV (Table 4).

Our findings are also in agreement with those of Voulgari *et al.* [21], who reported that in type 2 DM patients, CAN is independently associated with elevated BP, hyperglycemia, longer duration of diabetes, dyslipidemia, and

Table 1 Clinical findings in diabetes with CAN versus diabetics without CAN

	Present CAN ($N=70$) (%)	Absent CAN ($N=30$) (%)	P
Age (years)	54.4 ± 6.1	48.6 ± 4.1	<0.001
BMI (kg/m^2)	26.3 ± 1.2	26 ± 1.1	0.226
Duration of DM	9.9 ± 3.1	7.3 ± 1.1	<0.001
Resting heart rate	94 ± 8	92 ± 6	0.172
Postural hypotension [*N* (%)]	34 (48.57)	2 (6.66)	<0.001
Symptoms suggestive of CAN in other systems [*N* (%)]			
Gastrointestinal	4 (7.1)	1 (3.3)	0.88
Urogenital	20 (28.6)	3 (10)	0.044
Sudomotor (dry feet)	8 (11.4)	3 (10)	0.84
Peripheral neuritis	56 (80)	6 (20)	<0.001
Dry skin	42 (60)	3 (10)	<0.001
SBP	130 ± 5	120 ± 5	<0.001
DBP	80 ± 4	75 ± 5	<0.001
Mean pulse pressure	50.5 ± 3	45.5 ± 2	<0.001
Treatment of DM			
Oral	21 (30)	9 (30)	1
Combined oral and insulin	49 (70)	21 (70)	1

CAN, cardiac autonomic neuropathy; DBP, diastolic blood pressure; DM, diabetes mellitus; SBP, systolic blood pressure.

Table 2 Biochemical findings in diabetes with CAN versus diabetics without CAN

	Present CAN ($N=70$)	Absent CAN ($N=30$)	P
FBG (mg/dl)	180 ± 10	138.6 ± 4.1	<0.001
After 75 g glucose challenge (mg/dl)	310 ± 9	260 ± 1.1	<0.001
HbA1-c%	10.2 ± 1.1	9.2 ± 1.1	<0.001
Serum cholesterol (mg/dl)	198 ± 16	193 ± 30	0.39
Serum triglyceride (mg/dl)	189 ± 11	180 ± 8.0	<0.001
Serum uric acid (mg%)	6.9 ± 1.2	6.1 ± 1.9	0.035
Serum creatinine (mg)	1 ± 0.35	1.1 ± 0.2	0.074
Urine 24 h albumin excretion (mg/24 h)	130 ± 1.2	105 ± 1.1	<0.001
HB (g%)	10.9 ± 0.2	10.8 ± 0.3	0.097
Serum TSH	1.8 ± 0.4	1.7 ± 0.5	0.334

CAN, cardiac autonomic neuropathy; FBG, fasting blood glucose; HB, haemoglobin; TSH, thyroid stimulating hormone.

Table 3 Prevalence of CAN by the different assessment tests

Methods	*N* (%)
HRV: ↓E/I ratio	20 (20)
HRV: ↓Standing to lying flat	20 (20)
HRV: Valsalva maneuver	30 (30)
Postural hypotension	34 (34)
QTc prolongation > 460 mm	42 (42)
QTd > 10 ms	42 (42)

CAN, cardiac autonomic neuropathy; E/I, expiration to inspiration ratio; HRV, heart rate variability.

Table 4 ECG findings and transthoracic Doppler echocardiography in diabetics with CAN versus diabetics without CAN

	[*N* (%)]		
	Present CAN ($N=70$) (%)	Absent CAN ($N=30$) (%)	P
QTc interval ≥ 460 ms	42 (60)	10 (33.3)	0.01
QTd ≥ 10 ms	42 (60)	10 (33.3)	0.01
Evidence of LVH	28 (40)	3 (10)	0.003
LVM index ≥ 126 g/m^2	50 (70.1)	10 (33.3)	<0.001
E/A ratio < 1	40 (57.1)	10 (33.3)	0.029
EF > 60%	60 (85.7)	26 (86.6)	0.599

CAN, cardiac autonomic neuropathy; EF, ejection fraction; E/A, early peaking/atrial contraction; LVH, left ventricular hypertrophy; LVM, left ventricular mass.

Table 5 Clinical, biochemical, and ECG findings of cases with subclinical mild CAN versus severe CAN cases

	Mild CAN (*N*=18)	Severe CAN (*N*=52)	*P*
Age (years)	56.9±2.1	55.1±2.5	0.003
BMI (kg/m^2)	26.6±1.2	27.2±1.1	0.066
WC	95±3.5	96±4.1	0.321
Duration of DM	9.8±3.1	9.9±1.1	0.893
SBP	138±5	140±5	0.148
DBP	88±4	90±5	0.091
Mean pulse pressure	74.5±4	75.5±3	0.335
Resting heart rate	96±8	99±6	0.149
Postural hypotension [*N* (%)]	2 (11.1)	32 (64)	<0.001
HbA1-c	8.9±1.1	10.3±1.1	<0.001
Serum cholesterol (mg/dl)	205±10.2	210±8.9	0.068
Serum triglyceride (mg/dl)	199±8.1	201±7.1	0.355
Serum uric acid (mg%)	6.6±1.2	7.1±2.2	0.233
Serum creatinine (mg)	1.0±0.2	1.2±0.1	<0.001
Urine 24 h albumin excretion	190±1.2	200±1.2	<0.001
QTc interval	448.1±9.9	460.1±10.1	<0.001
QTd>10 ms [*N* (%)]	6 (33.3)	30 (57.7)	0.076
Evidence of LVH [*N* (%)]	6 (33.3)	30 (57.7)	0.076

CAN, cardiac autonomic neuropathy; DBP, diastolic blood pressure; DM, diabetes mellitus; LVH, left ventricular hypertrophy; SBP, systolic blood pressure; WC, waist circumference.

the presence of microvascular complications [21,32]. Katsilambros *et al.* [1] reported the association of high serum uric acid level and sudomotor dysfunction in patient with type 2 DM and CAN. In the present study, similarly, serum uric acid showed significant differences.

Symptoms of orthostatic intolerance and gastrointestinal function, urinary frequency, nocturia, and anhydrosis have been reported more frequently in diabetics with CAN. This is in agreement with Gibbons and Freeman [22], although in the present study, only the urogenital symptoms were significantly more frequent in the CAN group (Table 5).

Peripheral neuropathy was present in 80% of the patients examined. This is in agreement with Vinik and Ziegler [19], Gandhi *et al.* [33], who found that combined indices of autonomic and peripheral neurological dysfunction are associated with earlier CAN detection [34,35]. In the EURODIAB [24] prospective complication study, peripheral and autonomic neuropathy were among the strongest risk markers exceeding the effects of traditional risk factors.

Orthostatic hypotension was found in 34% of all the patients studied and in 60% of patients in the CAN group. Orthostatic symptomatology such as light headedness, dizziness, fatigability, and faintness on standing was very frequent (60%). However, no reported cases of clear or near syncope were reported. Orthostatic hypotension in CAN is secondary to efferent sympathetic vasomotor denervation, causing reduced vasoconstriction of the splanchnic and other peripheral beds [20].

In the present study, the resting heart rate in the CAN group was around 100 bpm, but was insignificantly rapid than in the non-CAN group. This is in agreement with the study of Pop-Busui *et al.* [17], who reported that increased resting heart rate is not a reliable diagnostic criterion for CAN in the absence of other signs.

In the present study, QTc prolongation and the more prevalent QTd are in agreement with Voulgari *et al.* [4]. The QTc interval is considered as a marker of cardiac autonomic dysfunction and is significantly associated with LVH [4]. The increase in the number of abnormal CAN function tests increases the risk further [36]. Pappachan *et al.* [37] concluded that the QTc interval can be used to diagnose CAN and the combined abnormalities of HRV, QTc, and QTd were strong predictors of mortality independent of conventional risk factors [38,39].

Prolongation of the QTc interval was detected in 60% of the CAN cases. This is in agreement with the finding of Lombardi [40]. LVH was significantly manifest in the CAN group in comparison with the non-CAN group.

In the present study, QTc interval prolongation (>440 ms) has been associated with increased age and duration of DM, SBP, DBP, mean pulse pressure, and severity of autonomic neuropathy. This is in accordance with the finding of Ewing *et al.* [41] and Veglio *et al.* [42].

Comparison of mild CAN cases and severe CAN cases showed some clinical, biochemical, electrocardiographic, and echocardiographic significant differences including older age, more postural hypotension, elevated HbA1-c, serum creatinine, urine 24 albumin excretion, and more frequent QTc prolongation, which may lead to greater CV risk.

Conclusion

CAN in women with type 2 DM is common. Detection of CAN irrespective of its scoring in patients with DM is important and can help exercise more precautions during their diabetic management. As patients with prolonged QT intervals are at a higher risk of sudden cardiac death, cases with severe CAN have to be screened for coronary artery disease preoperatively and special clinics for CAN may be warranted.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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