Study of the prevalence of cardiovascular autonomic neuropathy in Egyptian people with type 2 diabetes mellitus

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Background
Diabetes is a metabolic disorder characterized by chronic hyperglycemia and has long standing complication including both micro and macro vascular ones. One of the common underdiagnosed complications of diabetes is cardiovascular autonomic neuropathy (CAN), which encompasses damage to the autonomic nerve fiber that innervates the heart and blood vessels.
Objective
The aim of this work was to assess the prevalence of CAN in Egyptian people with type 2 diabetes.
Patients and Methods
The study was conducted on 120 subjects with type 2 diabetes. CAN was assessed by a group of defined cardiovascular autonomic reflex tests including (Resting heart rate, Heart rate response to standing, Beat-to-beat HRV, Blood pressure response to standing, Diastolic blood pressure response to isometric exercise and QTc interval). Patients with CAN were subsequently divided into three groups, Early, Definite and severe CAN.
Results and Conclusion
The prevalence of CAN is high in Egyptian people with type 2 diabetes amounting to 60%. Percentage of patients that had early, definite and severe CAN was 15%, 36.7% and 8.3% respectively. Positive significant independent correlation was found between CAN, HbA1c and serum total cholesterol.

Keywords:
Cardiac autonomic neuropathy, diabetes complications, egyptians people, type 2 DM

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Introduction

Diabetic autonomic neuropathy is a common diabetes complication that may affect different organ systems such as cardiovascular, gastrointestinal, genitourinary, sudomotor, and visual [1]. Cardiovascular autonomic neuropathy (CAN), within the context of diabetic autonomic neuropathy, occurs when there is an impairment of autonomic control of the cardiovascular system [2]. It results from damage to the autonomic nerve fiber that innervates the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics [3]. CAN is often overlooked in both diagnosis and treatment because there is no widely accepted single approach to its diagnosis [4].

Diabetic neuropathies, including CAN, are frequent chronic complications of diabetes that influence quality of life and have potentially fatal outcomes [5]. Prevalence rates between 1.6 and 90% have been reported, varying according to the diagnostic methods used, population studied, and disease stage [6]. Prevalence rates of CAN increase with age and duration of diabetes mellitus (DM). The Diabetes Control and Complication Trial reported rates as high as 35% in type 1 DM and 44% in type 2 DM, with a prevalence rate of up to 60% in longstanding diabetics [7].

CAN embraces orthostatic hypotension, exercise intolerance, intraoperative cardiovascular liability, and silent myocardial ischemia, which can result in life-threatening outcomes with increased cardiovascular morbidity and mortality [8–10]. It has been recognized that resting tachycardia and fixed heart rate are characteristic finding in diabetic patients with advanced CAN [11]. QTc interval has been considered as a marker of cardiac autonomic dysfunction and has been demonstrated as an independent predictor of CV mortality in patients with type 2 diabetes [10]. American diabetes association recommends yearly screening of autonomic neuropathy in patients with type 2 diabetes from the time of diagnosis [6].

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Cardiovascular autonomic reflex tests (CARTs) is most commonly used for the diagnosis of CAN based on heart rate variation (HRV) assessment [12]. In the 1970s, Ewing *et al.* [12] proposed five simple noninvasive tests to measure cardiac autonomic function based on the heart rate (HR) and blood pressure response to certain physiological maneuvers. These tests include the following.

The HR response to deep breathing, which assesses beat-to-beat HRV (R-R variation) during paced deep breathing [expiration to inspiration ratio (E : I)]; the HR response to standing, which is expressed as the 30 : 15 ratio, which is the ratio of the longest R-R interval (between the 20th and 40th beat) to the shortest R-R interval (between beats 5 and 25) elicited by a change from horizontal to vertical position; the Valsalva maneuver, which evaluates the HR response during and after a provoked increase in the intrathoracic and intra-abdominal pressures (the patient normally exhales for a period of 15 s against a fixed resistance); the blood pressure response to standing, which assesses the baroreflex-mediated blood pressure change following postural change; and the blood pressure response to sustained handgrip, as defined by the diastolic blood pressure increase caused by the sustained muscle contraction with the use of a handgrip.

The first two tests reflect defects in the parasympathetic activity, whereas the last two also describe changes in the sympathetic function [13,14]. The autonomic changes that occur during the Valsalva maneuver are complex and involve both the sympathetic and parasympathetic systems [15].

According to the CAN Subcommittee of the Toronto Consensus Panel statement following the 8th international symposium on diabetic neuropathy [16], the criteria for diagnosis and staging of CAN are as follows.

A single abnormal CART result is sufficient for the diagnosis of possible or early CAN, the presence of two or more abnormal tests is required for the diagnosis of definite or confirmed CAN, and the presence of orthostatic hypotension in addition to the aforementioned criteria signifies the presence of severe advanced CAN.

There is paucity of data about prevalence of CAN in Middle East generally and Egypt specifically. This invited us to conduct the current research to assess the prevalence of CAN among a sample of Egyptian people with known Type 2 diabetes.

Patients and methods

Patients were recruited from the outpatient clinic of the Diabetes Unit, Alexandria Main University Hospital. The study was carried out on 120 patients with type 2 diabetes. The study was conducted in accordance with the Declaration of Helsinki and the ICH Guideline for Good Clinical Practice. It was approved by the Ethics Committee of the Alexandria Faculty of Medicine. Exclusion criteria included hypotension; congestive heart failure; ischemic heart disease; cardiac dysrhythmia; endocrinal diseases that can affect heart rate and blood pressure, for example, hyperthyroidism and pheochromocytoma; chronic renal failure; and patients on medications such as vasodilators, anti-arrhythmic, hormonal treatment, beta-blockers, alpha-agonists, or alpha-blockers.

Written informed consent was obtained from all patients. All patients were subjected to full history taking including detailed analysis of different cardio-metabolic risk factors (family history of premature coronary artery disease (CAD), smoking, diabetes, hypertension, or dyslipidemia), postural hypotension, exercise intolerance, palpitation, and detailed drug history. Complete physical examination was done including full neurological examination. Laboratory investigations after 10–12 h overnight fasting included fasting blood sugar (FBS), glycated hemoglobin (HbA1C), total cholesterol (TC), high-density lipoprotein, low-density lipoprotein (LDL), urinary albumin to creatinine ratio, blood urea, and serum creatinine.

All patients were given the following instructions and precautions: avoid strenuous exercise 24 h before testing; avoid consumption of coffee and smoking before testing; avoid testing just after main meals; avoid testing in the presence of intercurrent diseases associated with fever, infection, or dehydration; and avoid testing during hypoglycemia.

After explaining the different maneuvers, the patients were tested for the following: resting heart rate (RHR) (a RHR of more than 100 beats per minute will be considered abnormal) [6], heart rate response to standing (during ECG monitoring, the R-R interval is measured at beats 15 and 30 after standing from supine. Normally, a tachycardia is followed by reflex bradycardia. The 30 : 15 ratio is >1.03) [6], beat-to-beat HRV (with the patient at rest and supine, heart rate is monitored by ECG while the patient breathes in and out at six breaths per minute. A difference in heart rate of >15 bpm is normal and <10 bpm is abnormal) [6], orthostatic

hypotension (blood pressure will be measured using sphygmomanometer in supine position and then the patient will be instructed to standup. Blood pressure will be measured again after 2 min of standing. Normal response is a fall in systolic blood pressure of <10 mmHg, borderline is a fall of 10–29 mmHg, and abnormal is a fall of >30 mmHg) [6], diastolic blood pressure response to isometric exercise (the blood pressure of the patient will be measured in supine position. The patient will be instructed to squeeze a small ball in his/her hand for about 5 min while lying on the bed and then blood pressure will be measured in the other hand again. An increase in diastolic blood pressure <16 will be considered abnormal) [6], and ECG recording (QTc interval >440 or prolonged ms will be considered abnormal) [6].

The interpretation of the result of the tests was as the following: early CAN if one abnormal result or two borderline results [17], definite CAN if two or more results are abnormal [17], and severe CAN if orthostatic hypotension is present [17].

Results

The studied group of 120 patients with type 2 diabetes included 50 (41.7%) males and 70 (58.3%) females. The mean age was 50.43±8.01 years. Number of patients with duration of diabetes 5 years or less was 70 (58.3%), from 5 to 10 years was 22 (18.3%), whereas the number of patients with duration of diabetes above 10 years was 28 (23.3%). The mean duration of diabetes was 6.32±5.70 years.

Resting heart rate

Although RHR was normal (<100) in 104 (86.7%) participants, 16 (13, 3%) participants had abnormal RHR (>100). The mean RHR was 82.80±13.23.

Beat-to-beat heart rate variations

The number of patients with normal, borderline, and abnormal HRV was 48 (40%), 14 (11.7%), and 58 (48.3%), respectively. Normal, borderline, and abnormal were defined as differences >15, 11–14, and <10 beats. The mean HRV was 12.08±5.42 beats.

RR interval at beats 15 and 30

According to RR interval at beat 15 : 30 ratio, 82 (68.3%) patients were normal (30 : 15 ratio, >1.03) and 38 (31.7%) were abnormal (30 : 15 ratio, <1.03).

Postural hypotension

Ten (8.3%) of the studied participants had postural hypotension as defined as systolic drop more than 30 mmHg. Twenty (16.7%) patients were borderline (systolic drop 10–29) and 90 (75%) patients were normal (systolic drop <10).

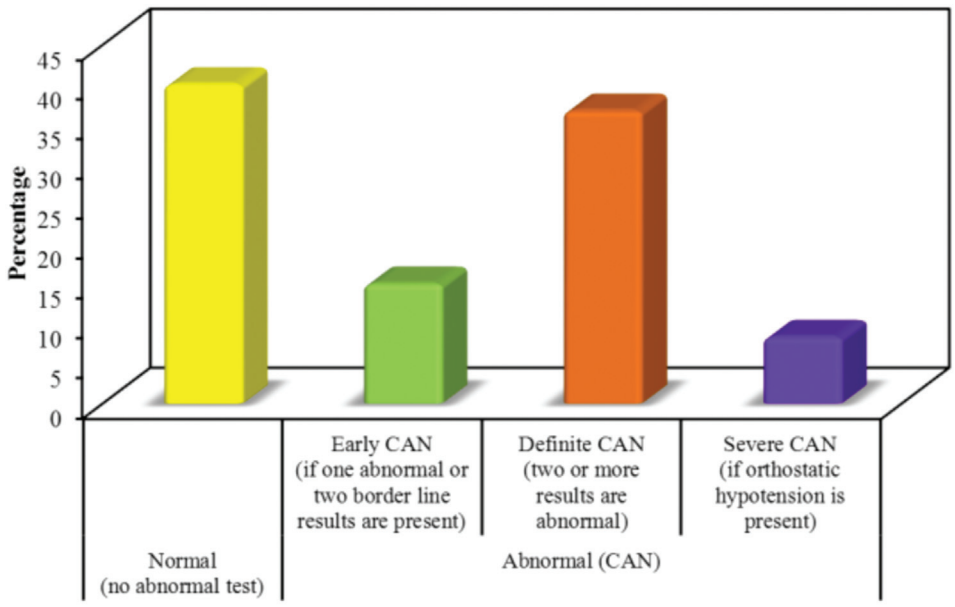
Diastolic blood pressure response to exercise

Normal diastolic blood pressure response (increase >16) was observed in 74 (61.7%) of the studied group, whereas abnormal response (increase <16) was observed in 46 (38.3%) of the studied group.

QTc interval

One hundred (83.3%) had got a normal QTc interval (<440) whereas only 20 (16.7%) patients had

Figure 1



Distribution of the studied cases according to prevalence of CAN (n=120).

prolonged QTc (>440). The mean QTc was 412.2 ±25.38.

Prevalence of cardiovascular autonomic neuropathy

Although 48 (40%) patients were normal regarding CAN prevalence, 72 (60%) patients were abnormal, and these were subsequently divided into three groups: early (if one abnormal or two borderline results are present), definite CAN (two or more results are abnormal), and severe CAN (if orthostatic hypotension is present). The number of patients who had early, definite, and severe CAN was 18 (15%), 44 (36.7%), and 10 (8.3%), respectively (Fig. 1).

Laboratory investigations

Table 1 shows descriptive analysis of the studied participants according to laboratory investigations. The mean HbA1C, FBS, and albumin to creatinine ratio were 8.98±1.84, 191.05±71.69, and 75.97±202.3, respectively, whereas the mean urea, creatinine, and TC were 28.53±7.48, 0.78±0.18, and 197.9±33.23, respectively. Mean LDL was 118.8±25.65 and mean high-density lipoprotein was 47.60±6.80 (Table 1).

Table 1 Descriptive analysis of the studied cases according to laboratory parameters (*n*=120)

Laboratory parameters	Min.–max.	Mean±SD	Median
HbA1C	6.0–13.80	8.98±1.84	8.75
FBS	72.0–431.0	191.05±71.69	71.69
ACR	4.60–1247.0	75.97±202.3	18.50
Urea	12.0–48.0	28.53±7.48	28.50
Creatinine	0.40–1.20	0.78±0.18	0.79
TC	130.0–288.0	197.9±33.23	192.5
LDL	64.0–200.0	118.8±25.65	117.5
HDL	32.0–64.0	47.60±6.80	47.0

ACR, albumin to creatinine ratio; HbA1C, glycated hemoglobin; HDL, high-density lipoprotein; FBS, fasting blood sugar; LDL, low-density lipoprotein; Max., maximum; Min., minimum; TC, total cholesterol.

Univariate and multivariate analyses of risk factors for cardiovascular autonomic neuropathy

Table 2 shows univariate and multivariate analyses for parameters considered to be risk factors for CAN in our study. According to univariate analysis, significant parameters were age, duration of illness, HBA1C, FBS, creatinine, TC, and LDL ($P<0.001$). Multivariate analysis was done only to significant univariate parameters and of those only HbA1C and TC were significant (Table 2).

Discussion

CAN is a common underdiagnosed complication of DM [1,18]. The effect of CAN on patients with DM can be devastating. CAN is shown to be associated with increased morbidity, CVD, chronic kidney disease, and mortality of DM [19,20]. CAN is probably underdiagnosed because of the lack of a universally accepted common diagnostic method. We have conducted a study aiming to estimate the prevalence as well as the risk factors of CAN among Egyptian patients with type 2 diabetes.

According to our results, the prevalence of CAN was 60%. Percentage of patients who had early, definite, and severe CAN was 15, 36.7, and 8.3%, respectively. Many studies have evaluated the prevalence of CAN in patients with type 2 diabetes, and the results had a wide range of variability. Matched with our results, Chen *et al.* [21], Menon *et al.* [22], Prasad *et al.* [23], and Domuschiev [24] have found the prevalence of CAN to be 60.6, 66, 58, and 59.5%, respectively, among patients with type 2 diabetes. Chen *et al.* [21]

Table 2 Univariate and multivariate analyses for the parameters affecting cardiovascular autonomic neuropathy (*n*=120) for the total sample

	Univariate		Multivariatea	
	P	OR (95% CI)	*P*	OR (95% CI)
Sex (female)	0.450	1.330 (0.635–2.786)	–	–
Age (years)	<0.001*	1.116 (1.055–1.180)	0.063	1.086 (0.995–1.184)
Duration	<0.001*	1.268 (1.145–1.405)	0.099	1.120 (0.979–1.282)
HbA1C	<0.001*	2.208 (1.603–3.043)	0.003*	2.189 (1.296–3.699)
FBS	<0.001*	1.015 (1.008–1.022)	0.854	0.999 (0.987–1.011)
ACR	0.063	1.026 (0.999–1.055)	–	–
Urea	0.590	1.014 (0.965–1.065)	–	–
Creatinine	0.007*	22.499 (2.354–215.006)	0.518	0.234 (0.003–19.173)
TC	<0.001*	1.046 (1.027–1.064)	0.002*	1.076 (1.027–1.128)
LDL	<0.001*	1.052 (1.029–1.075)	0.109	0.960 (0.912–1.009)
HDL	0.644	1.013 (0.959–1.069)	–	–

ACR, albumin to creatinine ratio; CI, confidence interval; HbA1C, glycated hemoglobin; HDL, high-density lipoprotein; FBS, fasting blood sugar; LDL, low-density lipoprotein; OR, odds ratio. [a]All variables with *P* value less than 0.05 were included in the multivariate analysis.
*Statistically significant at *P* value less than or equal to 0.05.

included a larger sample than ours (431 men and 181 women with type 2 diabetes). They found that the prevalence rate of CAN tests was 46.1% in patients with the history of diabetes less than 5 years and up to 69.4% when the history of diabetes exceeded 20 years. Additionally, they calculated the 8-year survival rate for patients with CAN and found it to be 63.6% in males and 76.4% in females, so they concluded that CAN was associated with high rates of mortality. Menon *et al.* [22] studied CAN in 74 patients and found a high prevalence of abnormal CARTs, sustained handgrip of 81%, E: I ratio of 66.2%, 30 : 15 ratio of 28.3%, and orthostatic hypotension of 13.5%. They estimated possible CAN prevalence to be 31.0% and definite CAN 66.2%. They found that only ten patients had advanced CAN. Domuschiev [24] studied a smaller sample (42 patients) with type 2 diabetes. Regarding studied tests, he found the following: orthostatic hypotension in eight (19%), abnormal Valsalva ratio in 12 (28.6%), abnormal heart rate response to deep breathing in 14 (33.3%), and abnormal heart rate response to standing (30 : 15 ratio) in 13 (31%) patients. Furthermore, they did fundus examination and found a positive link of cardiac autonomic neuropathy with proliferative retinopathy in type 2 diabetics.

Some studies did disagree with us showing lower prevalence of CAN. Mansour *et al.* [25], Eze *et al.* [26], and Tahrani *et al.* [27] showed the prevalence of CAN to be 42.6, 44.3, and 42.2%, respectively. However, others have found a higher prevalence of CAN than ours. Khoharo and Qureshi [28], Low *et al.* [29], Mendivil *et al.* [30], Refaie [31], and Hassan *et al.* [32] had estimated prevalence of 70, 73, 68, 70, and 72%, respectively.

The possible explanation to this huge variation in CAN prevalence is the inconsistency in the criteria used to diagnose CAN and significant differences in the study populations, particularly in relation to CAN risk factors (such as age, sex, and DM duration amongst others).

Regarding risk factors for CAN in patients with type 2 DM, our results showed that age, duration of illness, HBA1C, FBS, creatinine, TC, and LDL were significantly related to CAN using univariate analysis. When we used multivariate analysis, only HbA1C and TC were significant. Ziegler [33], Rolim *et al.* [34], Boulton *et al.* [6], and Valensi *et al.* [35] totally agreed with our results in defining risk factors of CAN. Although these studies differed from our study in the number of patients and tests used, they agreed with our results in all risk factors.

However, many other studies disagreed with us in one or more risk factors. Pop-Busui *et al.* [36] mismatched our results regarding sex as a risk factor for CAN. In their study that was conducted on 8000 patients, they found that CAN was more prevalent in women (2.2% in women and 1.4% in men for severe; 4.7% in women and 2.6% in men for moderate to severe). Pappachan *et al.* [37] performed a cross-sectional study on patients attending the diabetic clinic of a teaching hospital. They found that significant risks for CAN among patients with type 2 diabetes were coexistent peripheral neuropathy [odds ratio (OR=14)], prolonged QTc (OR=9.75), higher age (OR=7.2), and disease duration over 10 years (OR=1.92) in univariate analysis, but none of them showed independent risk in multivariate analysis. Arif *et al.* [38] conducted a cross-sectional study on 204 patients. They found the only significant risk factor for CAN development was poorly controlled blood glucose (HBA1C). Bhalerao *et al.* [39] was a multicenter study carried out in India. They concluded that age, duration of diabetes, sex, and diet were significantly associated with prevalence of CAN estimated by HRV analysis. Voulgari *et al.* [40] found that longer duration of diabetes and presence of microvascular complications were the only independent risk factors associated with CAN development, whereas Knuiman *et al.* [41] found that only duration was the independent factor.

Refaie [31] found that QTc prolongation was significantly related to age. Khoharo and Qureshi [28] disagreed with our results as they found that CAN was related to duration of diabetes but not the control of hyperglycemia. All their participants being poorly controlled may be the explanation to these results. Only age and duration were found to be independent risk factors for CAN by Hassan *et al.* [32].

Conclusion and Recommendations

CAN is a common, but usually overlooked, diabetic complication in our Egyptian population. Health care professional should be prudent to screen for it. HbA1C and cholesterol level independently affect the occurrence of CAN.

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Conflicts of interest

There are no conflicts of interest.

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