

# The association between cardiac autonomic neuropathy and diabetes control

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*Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*

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**Introduction:** Cardiac autonomic neuropathy (CAN) is one of major complications of diabetes mellitus (DM) that increases the risk of cardiovascular disorders, abnormal ventricular depolarization with poor prognosis as well as increased mortality and morbidity. Indeed, CAN has close relation with blood glucose level in diabetic patients. We investigated the relation of CAN with diabetes control.

**Materials and methods:** Totally, 115 diabetic patients (mean age 50.87±13.90 years old; 78 females) underwent study. All patients had DM and cardiac sinus rhythm. Nobody had sickness affecting cardiac rhythm and blood pressure. In addition, they did not take drugs that had effect on blood pressure, cardiac rhythm, and QT interval. Forty-six patients had tight and 69 patients had uncontrolled DM according to American Diabetes Association (ADA) criteria. The CAN was assessed based on heart rate variation during physical examination (at rest tachycardia and orthostatic hypotension) and standard Ewing's tests (deep-breathing and laying-to-standing tests) with bedside continuous ECG recording. The *P*-value <0.05 is considered significant.

**Results:** Seventy-five patients (65.2%) had CAN. In patients with CAN, 13.9% were symptomatic and 51.3% were asymptomatic. Resting tachycardia and hypotension were found in 5.2%, 8.7% of patients, respectively. Abnormal deep-breathing and laying-to-standing tests were found in 73% and 71.3% of asymptomatic patients, respectively. CAN was more prevalence at uncontrolled DM (67.3% vs 63.7%) but the difference was not significant. The prevalence of CAN had direct association with duration of DM in both tight and uncontrolled groups (*P*<0.05). The mean of age, sex, and type of treatment had no association with CAN prevalence.

**Conclusion:** The prevalence of CAN, especially asymptomatic type, was high. Its prevalence was increased with prolonged duration of DM. But we did not find any relationship between CAN and glycemic control level.

**Keywords:** cardiac autonomic neuropathy, diabetes mellitus, glycemic control, diabetic autonomic neuropathy, Hb A1c, electrocardiogram

## Background

One of the most common metabolic abnormalities with high morbidity and mortality rates around the world is diabetes mellitus (DM).<sup>1</sup> It has chronic complications and involves various organs in body such as autonomic nervous system and cardiovascular system.<sup>1</sup> The prevalence of cardiac autonomic neuropathy (CAN) in diabetic patients is about 10% in symptomatic cases and its prevalence reaches 100% in the asymptomatic cases with accurate methods such as radionuclide scan.<sup>2-4</sup> The (CAN) without symptoms has

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high prevalence. It causes problems in sense of chest pain, changes in ischemic threshold, problems in ventricle systolic and diastolic function, increased chances of cardiac arrhythmia, changes in circadian rhythm of body blood pressure, cardiac events such as sudden death, infarction, exacerbation of silent myocardial ischemia and exercise intolerance.<sup>2-4</sup> This complication in anesthesia and surgery causes problems in insertion of tracheal tube, increased chance of pulmonary aspiration due to residual food in the stomach caused by gastroparesis, arrhythmia resistant to treatment, sudden cardiac arrest, and hypotension which is resistant to treatment. In addition, this complication has direct relationship with other diseases in diabetic patients such as small vessel disease in kidney, eye. Also, it can affect the nervous system and other organs such as digestive and genitourinary systems.<sup>5</sup>

The precise control of blood pressure, weight loss, treatment with hypotensive blood pressure anti-arrhythmic drugs, prevents the progression of these conditions.<sup>6</sup> Also, the search for premature ventricular reperfusion, silent ischemia in patients with other risk factors for coronary artery disease prevents progression of this condition. Moreover, it will reduce the risk and complications of surgery and anesthesia before, during and after surgery. The diagnosis of autonomic neuropathy can be used to predict and diagnose other complications of diabetes such as gastroparesis which is difficult to diagnose.<sup>7</sup>

According to the lack of previous detailed investigations on this syndrome, this study aimed to identify the prevalence and relationship of cardiac autonomic neuropathy with blood glucose levels in diabetic patients.

## Materials and methods

This study was a descriptive cross-sectional study which was performed on diabetic patients who referred to internal medicine or endocrine clinic of Loghman Hakim General Hospital, Tehran, Iran. All patients who referred to the two clinics during one year were entered into the study according to inclusion and exclusion criteria. Inclusion criteria: diabetic patients who have cardiac sinus rhythm and stable vital sign; exclusion criteria: presence of any symptoms of anemia, hypoxia, hypovolemia, sepsis, renal failure and other diseases that affect heart rhythm and orthostatic hypotension; Patients who take medications that affect cardiac rhythm, QT intervals and blood pressure eg: calcium channel blockers and beta

receptors, except angiotensin converting enzyme inhibitors and angiotensin receptor blocking agent; anti-arrhythmic drugs and triangular antidepressants, phenothiazine

This research has been reviewed at the Ethics Committee of the Medicine Faculty of Shahid Beheshti University of Medical Sciences and has been approved in accordance with the Helsinki Statement. This research has been designed and implemented according to the recommendations of this committee.

After obtaining written consent, patients were interviewed and examined by an internal medicine resident. The first clinical exam was performed in a fasting state and other evaluations were conducted from 09:00 to 16:00, at least 2 hours after waking up.<sup>8,9</sup> Weight was measured with a digital scale with 100 g accuracy with minimum clothes and height were measured with a metal stadiometer with a precision of 0.5 cm in standard standing position without shoes. Blood pressure was measured after 15 minutes of rest with a standard mercurial sphygmometer from the right hand in the sitting position. Then, 10 cc of venous blood was taken from the patient after 12 hours of fasting. All specimens were stored in Vacutainer's single-use test tubes (KIMO brand, Italy) at  $-20^{\circ}\text{C}$  and tests were done at the end of each week. Blood glucose, total cholesterol, triglyceride, high and low density lipoprotein cholesterol were measured by enzymatic flowmetry (Random Kit, UK).

A questionnaire containing demographic information was completed. Then the blood pressure and heart rate of the right hand examined in lying down (15 minutes rest) and standing positions. Later on, the continuous electrocardiogram (ECG) was taken from each individual in two modes:<sup>4,10,11</sup>

1. The patient breathed deeply 6 times per minute, and the ECG was taken continuously for 1 minute in supine position. The time of inspiration and expiration was marked on the ECG tape.
2. The ECG was taken continuously for 1 minute in standing position.

The RR intervals were calculated based on the continuous ECG tape.

Body mass index (BMI) was calculated by dividing the weight (kg) by height (m).<sup>2</sup>

Diagnosis of diabetes was based on American Diabetes Association criteria.<sup>12</sup> The patients were divided into two

groups, patients with tight controlled DM for at least 1 year (HbA1c <7%, BS 2 hours post prandial <180 mg/dl, FBS <130 mg/dl) and uncontrolled DM (without one of the above criteria).

The CAN was diagnosed based on standard Ewing's tests.<sup>4</sup> There are five bedside tests for cardiovascular reflexes and patients scored based on 0 to 5. The definite CAN was diagnosed based on at least two abnormal tests.

The patients who had orthostatic hypotension or at rest tachycardia were considered symptomatic CAN.<sup>4</sup>

#### Ewing's tests for diagnosis of CAN:<sup>4</sup>

1. At rest tachycardia; heart rate more than 100 beats per minute after 15 minutes of rest in supine position.
2. Beat-to-beat heart rate variability (HRV); in a patient who lies down and breathes 6 times per minute, if one of the following criteria exists, is considered abnormal.  
The expiration to inspiration RR interval ratio more than 1.17.  
Maximum heart rate minus minimum heart rate less than 10 beats per minute.
3. Heart rate response to stand up; when patient stands up, 30th to 15th R-R interval ratio less than 1.03 is considered abnormal.
4. Heart rate change after Valsalva maneuver; when a patient, by forced blowing into an oral piece of a manometer, can apply a force of 40 mm Hg for at least 15 seconds, longest and shortest RR intervals were measured.  
The longest to shortest RR interval ratio less than 1.2 is abnormal.
5. Orthostatic hypotension; first patient lies down then stands for 2 minutes and systolic blood pressure were measured.  
Reduction in blood pressure by 30 mmHg or more in standing position is considered abnormal.

## Statistical analysis

All information recorded in the questionnaire. Independent t-test was used to compare the quantitative variables. Chi-squared test was used for qualitative variables. Simple regression analysis was used to determine the relation of blood glucose level with each quantitative parameters of CAN. SPSS Version 13.1 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis and  $P < 0.05$  was considered as a significant level of difference.

## Result

During 1 year, 128 patients were examined, 8 patients were excluded from the study despite repeated follow-up because of incomplete tests and 5 patients were excluded due to incomplete ECGs. Finally, the data of 115 patients were analyzed. The mean  $\pm$ SD age of the patients was  $50.87 \pm 13.99$  years (14–78 years). Of these, 32.2% were male and 67.8% were female. The mean  $\pm$ SD duration of diabetes was  $77.43 \pm 77.22$  months (0 at least in newly diagnosed individuals and maximum 384 months). In these patients, 40% had tightly controlled DM and 60% had uncontrolled DM. In diabetic patients 61.7% received oral glucose-lowering tablets, 24.3% insulin, 2.6% combined treatments, 3.5% had only diet and 7.8% were not treated. There were no significant differences in age and sex in both groups ( $P=1$  and  $P=0.16$ , respectively). The basic characteristics of the participants are listed in Table 1.

In total, 65.2% patients had CAN and 34.8% had no CAN. Sixteen patients (13.9%) had symptomatic CAN (with resting tachycardia or orthostatic hypotension), and 59 patients (51.3%) had asymptomatic CAN. (5.2% at rest tachycardia; 8.7% orthostatic hypotension; 73% abnormal breathing test; 71.3% abnormal lying-to-standing test). Patients with and without CAN had no significant difference in age and sex ( $P=0.59$  and  $P=0.43$ , respectively).

There was no significant difference between the two groups in terms of controlling diabetes (tightly controlled or uncontrolled DM) and type of treatment with CAN ( $P=0.68$  and  $P=0.53$ , respectively). The mean  $\pm$ SD duration of diabetes in people with CAN was higher than those without CAN, ( $P=0.01$ ). (Table 2)

## Discussion

In summary, the data of 115 diabetic patients with mean age of 50 years, which were 67.8% female, were studied. In these diabetic patients 40% had tightly controlled and 60% had uncontrolled DM at least for 1 year. About two thirds of patients had CAN. The number of asymptomatic patients was almost four times symptomatic individuals. Generally, the average age was lower in those with CAN. There were more male, and patients with tightly controlled DM in this group, but these differences were not significant. Duration of diabetes was longer in people with CAN, and this relationship was significant. There was no significant difference in age and sex in the two groups.

**Table 1** Characteristic of the study subjects in patients with and without CAN

Variables	Patients with CAN	Patients without CAN	P-value
Age, years (mean $\pm$ SD)	50.41 $\pm$ 14.43	51.73 $\pm$ 13.24	0.59
Duration of DM (months)	94.83 $\pm$ 94.38	68.16 $\pm$ 65.15	0.01
Sex			0.43
Female	65.3%	72.5%	
Male	34.66%	27.5%	
BMI (Kg/m <sup>2</sup> )	28.06 $\pm$ 5.36	27.37 $\pm$ 4.22	0.05
Type of treatment (N)			0.53
No treatment	9	2	
Diet therapy	3	1	
OGLA	43	28	
Insulin	19	9	
Insulin + OGLA	3	0	
HbA1C (%)	8.14 $\pm$ 2.09	7.74 $\pm$ 10.77	0.2
Total cholesterol (mg/dL)	209 $\pm$ 39.84	203.72 $\pm$ 48.26	0.2
Triglyceride (mg/dL)	205.26 $\pm$ 152.35	189.4 $\pm$ 104.71	0.3
HDL (mg/dL)	44.56 $\pm$ 13.52	51.77 $\pm$ 30.44	0.5
LDL (mg/dL)	165.52 $\pm$ 95.56	119.78 $\pm$ 40.41	0.008

**Abbreviations:** CAN, cardiac autonomic neuropathy; DM, diabetes mellitus; BMI, body mass index; OGLA, oral glucose lowering agent; HbA1C, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein.

**Table 2** Frequency of CAN in terms of diabetes control in subjects

	Tightly controlled DM N (%)	Uncontrolled DM N (%)	Total
Patients with CAN (N=75)	31(46.2)	44(53.8)	75(100)
Patients without CAN (N=40)	15(37.5)	25(62.5)	40(100)

**Abbreviations:** CAN, cardiac autonomic neuropathy; DM, diabetes mellitus.

Neuropathy is the most prevalent complication of DM,<sup>13</sup> and our study based on cardiovascular reflexes (Ewing's tests), showed that CAN has a high prevalence (65.2%), which is often asymptomatic (51.3%). As reported in large studies, the incidence of CAN in diabetic patients can range from 17–90% in patients. For example, in patients with type 1 diabetes, an incidence of 27.5% and in patients with type 2 diabetes was 73%.<sup>14</sup> The prevalence of CAN in this study was consistent with the overall incidence of CAN in other studies, like 68% in the review of Mendivil in the US in 2016.<sup>15</sup>

In this study, the incidence of symptomatic CAN was 13.9% on the basis of orthostatic hypotension and resting tachycardia. Symptomatic CAN sometimes has a high

prevalence on the basis of the above criteria. The prevalence of this symptom in diabetics is 10% and increases with age to 16–20% which is consistent with our results.<sup>16,17</sup> In one study, postural hypotension had a prevalence of around 46%.<sup>18,19</sup>

CAN prevalence increases with the duration of the disease. In this study, the duration of diabetes in people with CAN was higher than those without CAN, which is consistent with some previous studies. In many studies such as Andrei and Amarin study, there was a direct relationship between the incidence of neuropathy and the duration of diabetes. Of course, depending on the type of diabetes, this relationship sometimes varies. In type 2 diabetes, This complication occurred earlier than type 1 diabetes.<sup>20</sup>

If we use more diagnostic criteria and more precise instruments, the prevalence is higher.

The prevalence of CAN in precise methods such as MIBG scan and PET scan is high.<sup>20–22</sup> We used a short-term continuous ECG. Its accuracy is less than 24-hour Holter monitoring of heart rate and blood pressure but is acceptable, noninvasive, and simple and can be done at the patient's bedside. Its sensitivity is 93–100% and specificity 69–75% in different studies. Though all interviews and examinations have been performed by the researcher herself, she is an assistant in the Internal Medicine Department. Moreover, the disadvantage of these tests is that they require the patient's cooperation or active participation, and are operator dependent.<sup>23</sup> Even the newly published studies also used ECGs less than 10 seconds long and had similar results. In very short duration continuous ECG like 10-second duration, you cannot measure frequency amplitude but you can measure time domain.<sup>24</sup>

Heart rate variability (HRV) decreases with age. Of course, in some studies, the relationship between HRV and age is U-shaped, that is, the heart rate rises from birth to age 20 and then decreases slightly until about 40 years. After that, it reaches the Plato level and rises again from about 75 years of age.<sup>25</sup> In our study, no significant difference was seen between the two groups in terms of age and age groups at baseline characteristics. This eliminates the difference between the two groups and prevents the results from being altered due to age differences. The mean  $\pm$ SD age for CAN patients was lower than those without CAN, but this was not statistically significant. Other studies have shown that CAN is not related to age.<sup>26</sup> Although most studies showed a positive relationship between age and CAN prevalence. Part of this difference can be due to the age composition of the population studied. For example, in our study, 15% of people were aged less than 40 years old and 9% of those were aged over 70 years old.

There is a difference in HRV between men and women, although the difference between the two sexes decreases with age. The mechanism of making the difference between the two sexes is not precisely defined, but factors such as genetics, sex hormones, and underlying differences in cardiovascular parameters such as differences in baseline blood pressure are considered effective.<sup>27–29</sup> In our study like the Verona Newly Diagnosed Type 2 Diabetes Study (VNDS),<sup>29</sup> patients with CAN (either with precise control, or uncontrolled DM), the number of females has been higher than males, but this difference was not significant.

The prevalence of CAN was 53.8% in uncontrolled and 46.2% in patients with tightly controlled DM, but this difference was not statistically significant. The controlling of diabetes can prevent or delay the onset of microvascular complications and the cumulative incidence of diabetic neuropathy has a direct relationship with HbA1c level.<sup>30</sup> These differences can be due to several reasons that may affect the results such as criteria for tight control diabetes, duration of diabetes, metabolic memory, sample size, and diagnostic method for CAN.

We selected patients with HbA1c <7%, BS 2 hours post prandial <180 mg/dL, FBS <130 mg/dL for at least 1 year as tightly controlled DM.

First, different criteria have been used to define precise control of diabetes in various studies.<sup>31</sup>

Second, because HbA1c only shows the status of the last 3 months, and unfortunately most of our patients lack regular and valid medical history to determine the long-term status of diabetes control. The above criterion only indicates proper glucose control over the past year and does not indicate long-term control of DM in patients.

Third, the metabolic memory may also affect the results.<sup>32</sup>

The sample number of our study is low with shorter follow-up period compared to large studies and was conducted only in a single center.

We have used physical examination (pulse rate and blood pressure measurement in supine and standing positions) and continuous ECG for CAN diagnosis. At each stage of the diagnostic tests, a continuous ECG was taken for at least 1 minute.

Although the continuous ECG has a lower diagnostic accuracy than the 24-hour Holter monitoring, it is an easy, accessible, available and inexpensive test which can be done at the patient's bedside. This test has an appropriate sensitivity and specificity for the diagnosis of autonomic neuropathy. Several studies have shown the acceptable sensitivity and specificity of these tests, even when they are performed at a shorter time than 24 hours (for 10 seconds to 20 minutes).<sup>29,33,34</sup>

We used five tests for CAN diagnosis in all participants but other studies used two tests for suspicious participants who have had dizziness in standing, diarrhea at nights and incomplete bladder emptying.<sup>34–36</sup>

We did not evaluate other risk factors of neuropathy like hypertension, smoking, etc.<sup>37</sup> These factors may have affected our results.

This study had some limitation. First, this study had small sample size. Second a tightly controlled criterion for DM was considered for the 1 year, while long-term blood glucose control was unclear. Third, we did not evaluate other risk factors of neuropathy.

This study has several strengths. First, the examinations and diagnostic procedures were performed by a single person who increases the internal validity of tests. Second, all tests were performed throughout the day to eliminate circadian changes in heart rate variability and blood pressure. Third, we used five tests for CAN diagnosis. Fourth, in this research we used a cheap, accessible, easy and affordable tool at the patient's bedside. In remote and deprived areas that do not have access to advanced facilities such as cardiac Holter monitoring, all physicians and technicians can easily apply this technique and interpret its results.

In conclusion, this study showed CAN has high prevalence, especially asymptomatic CAN and its prevalence is increased with prolongation of disease. We did not find any relationship between CAN and glyce-mic control level. Because of the cross-sectional study it was not apparent how much time DM was controlled and we could not clarify long-term glyce-mic control. Cardio vascular reflexes (Ewing's Test) seem to be the primary technique in evaluation of CAN due to its low cost, easy use at the patient's bedside with good inter-individual reproducibility. Finally, the prevalence of CAN in different studies varies depending on the definition, diagnostic criteria, population of the study, diagnostic methods, duration of the disease, stage of disease, and so on.

## Ethics approval and consent to participate

This research has been reviewed at the Ethics Committee of the Faculty of Medicine of Shahid Beheshti University of Medical Sciences and has been approved in accordance with the Helsinki Statement. This research has been designed and implemented according to the recommendations of this committee.

## Consent for publication

The research subjects were interviewed and examined after obtaining written consent.

## Availability of data and material

The data are available from the authors upon reasonable request.

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## Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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