

ORIGINAL ARTICLE

Non-Invasive Diagnosis of The Cardiac Autonomic Neuropathy In Patients With Diabetes Mellitus

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ABSTRACT

Cardiac autonomic neuropathy (CAN) is a very common diabetes-related complication with rise of mortality and morbidity of patients with DM. Proper diagnosis of CAN with easy standard bedside tests in DM patients is critically important for early prophylaxes of further CV complications. To establish and compare the clinical and diagnostic characteristic of CAN among the DM I and DM II patients. We examined 75 patients with DM (DM I – 30, DM II – 45). CAN we diagnosed by cardiac autonomic reflex tests (CART): Evaluating of the resting tachycardia; Heart rate response to deep breathing; Valsalva maneuver; Systolic blood pressure response to standing; Diastolic blood pressure response to sustained handgrip. Absence of CAV we found out in near 40% of patients. 46,8% of patients were diagnosed with early and definitive CAN, with higher prevalence of definitive CAN in DM II patients. Severe CAN also developed more often in DM II patients. Coexistence of CAN and peripheral neuropathy was higher in DM I patients in 1,26 times. Among DM I patients with CAN only 11,8% persons had no sensory peripheral neuropathy, while 29,7% among DM II patients with CAN. Positive correlations presented between the DM history and manifestations of CAN in DM II patients; diabetic sensory polyneuropathy, retinopathy and CAN in DM I patients, with preceding of CAN to manifestations of peripheral neuropathy. Thus, the proposed set of diagnostic measures allows the timely diagnosis of CAN and objectively assessing the effectiveness of the therapy.

**Key words:** Cardiac Autonomic Neuropathy, Diabetes Mellitus, diagnosis.

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INTRODUCTION

Diabetes mellitus (DM) is a global epidemic affecting near 8.5% of the population and more than 370 million people all over the world with 50% undiagnosed cases. It is estimated that almost one in six people are currently at risk of developing diabetes related complications [1, 2]. Cardiovascular diseases (CVD) play a leading role in mortality and morbidity in patients with DM and the main goal of diabetes treatment is to reduce the development of CVD as well as the vascular complications associated with diabetes [3, 4].

Cardiac autonomic neuropathy (CAN) is a very common diabetes-related complication that has a major effect on CVD, mortality and morbidity in patients with DM [5, 6]. Based on the CAN Subcommittee of the Toronto Consensus Panel on Diabetic Neuropathy [7, 8], CAN is defined as the impairment of cardiovascular autonomic control in patients with established DM following the exclusion of other causes. The prevalence of CAN varies between 1% and 90% in patients with type I DM (DM I) and 20%-73% in patients with DM II [9, 10, 11]. CAN is divided into a sub-clinical and a clinical stage and can be detected by analysis of Heart Rate Variability (HRV) or standard cardiac autonomic reflex testing (CART) [12].

HR responses to deep breathing, standing and Valsalva maneuver, as well as blood pressure response to standing (CART) are considered as the gold standard in clinical testing for autonomic neuropathy [13, 14]. According to the CAN Subcommittee of the Toronto Consensus Panel statement following the 8th

international symposium on diabetic neuropathy in 2010 [8], criteria for CAN diagnosis and staging are: (1) one abnormal cardiovagal test result identifies possible or early CAN; (2) at least two abnormal cardiovagal test results are required for definite or confirmed CAN; and (3) the presence of orthostatic hypotension in addition to abnormal heart rate test results identifies severe or advanced CAN. Progressive stages of CAN are associated with increasingly worse prognosis.

Careful and timely testing of CAN with easy standard bedside tests in patients with DM I and II is critically important for early diagnoses and prophylaxes of further CV complications [15, 16].

To establish and compare the clinical and diagnostic characteristic of CAN among the DM I and DM II patients.

## MATERIAL AND METHODS

We examined 75 patients with Diabetes Mellitus (DM I – 30 patients, DM II – 45 patients) who were hospitalized to the endocrinology department for treatment (table 1). All patients were investigated routinely – complains, anamnestic data, objective examination, additional examination (blood test, sugar test, GTT, HbA1, urine test, ECG, other standard tests).

Table 1: Characteristic of patients

Points	DM type I	DM type II
No of patients	30	45
Mean age, years	30,21 ± 10,96	50,17 ± 8,84
Mean age of onset of DM, years	19,43 ± 7,7	43,18 ± 9,21
Male: Female ratio	17:13 (1,3:1)	17:28 (1:1,5)
Duration of the DM, years	11,34±7,76	8,33 ± 3,7
Mean BMI, kg/m <sup>2</sup>	23 ± 3,12	29,24± 6,18
Family DM history	7 (23,3%)	18 (40%)
History of the pancreatitis	8 (27,3%)	15 (30%)

Table 2: Cardiac autonomic reflex tests for diagnosis the cardiac autonomic neuropathy

Autonomic function test	Points
1. Resting heart rate	
<100 beats/min	0
100–110 beats/min	0,5
>110 beats/min	1
2. Postural hypotension (fall in systolic blood pressure)	
<20 mm Hg	0
20–30 mm Hg	0,5
>30 mm Hg	1
3. Valsalva ratio	
>1.2	0
1.2–1.10	0,5
<1.10	1
4. Heart rate response on deep breathing	
>15 beats/min	0
15–10 beats/min	0,5
<10 beats/min	1
5. Increase in diastolic blood pressure during sustained handgrip	
>15 mm Hg	0
15–10 mm Hg	0,5
<10 mm Hg	1

*Determination of the CAN. The total points from each of these five tests would be added together and the cardiac autonomic neuropathy score (CAN score) will be categorized as following: CAN score 0 (total points 0) - absent, CAN score 1 (points 0,5 – 1,5) - early, CAN score 2 (points 2–3) - definite, and CAN score 3 (points more than 3) - severe.*

Every participant was also examined for the presence or absence of peripheral neuropathy by testing for abnormal pin-prick sensations of the limbs, abnormality of position sense in the big toes, and the absence of Achilles' tendon reflex. Hypertensive patients and those with nephropathy were excluded from the study cohort because of their likelihood of having baseline ECG abnormalities and because these diseases may interfere with the autonomic function tests. For defining of CAN next five classical tests were done (cardiac autonomic reflex testing (CART)): Evaluating of the Resting tachycardia; Heart rate response to deep breathing; Valsalva maneuver; Systolic blood pressure response to standing; Diastolic blood pressure response to sustained handgrip (table 2).

## RESULT AND DISCUSSION

Most of the patients of DM I (46,7%) came to hospital for regular checkup, while only 6,5% of DM II were hospitalized for the same reason. Some patients (20 % DM I and 37% DM II) needed to be hospitalized due to complaints of uncontrolled glycaemia, hyposensation and pain of extremities, others (20% DM I and 43,5% DM II) came for standard diabetic complains and sings of diabetic complications. 13,3% of DM I patients and 11% of DM II patients were hospitalized firstly because of diagnoses of DM. Standard diabetic tests showed decompensation of DM in all patients (table 3).

Table 3: Results of routine diabetic tests

Tests	DM I patients	DM II patients
Mean HbA1c level, %	13,16 ± 3,48	12,1 ± 2,7
Mean fasting blood glucose, mmol/l	10,45 ± 2,48	10,4 ± 3,1
Glucose level in urine, mmol/l	25,5± 4,5	22,7± 5,1

Clinically 20% of DM I and 17,8% of DM II patients had palpitation, resting tachycardia, 10% of DM I and 11,1% of DM II patients felt dyspnea in physical exertions, 10% of DM I and 15% of DM II patients had weakness, dizziness, visual impairment from a lying to a standing posture (orthostatic hypotension). Clinical signs of CVD were defined in all firstly diagnosed DM II patients and in half of DM I patients. After providing 5 examination tests for diagnosis of CAN we analyzed next results (see table 4).

Table 4 : Positive results of the tests for determination of CAN

CAN tests	DM I patients	DM II patients
1) Resting tachycardia	6 (20%)	10 (20%)
2) Standing tests for orthostatic hypotension	10 (33%)	15 (30%)
3) Valsalva maneuver	9 (30%)	16 (35,5%)
4) Heart rate response to deep breathing	6 (20%)	8 (17,8%)
5) Diastolic blood pressure response to sustained handgrip	11 (37%)	20 (44,%)

Scoring of CAN in examined patients shown the next results (see table 5).

Table 5: Stages of CAN in DM patients

Stages of CAN with score	DM I patients	DM II patients
1) No CAN ( score-0)	13 (43.3%)	18 (40%)
2) Early CAN (score-1). Points 0,5 - 1,5	7 (23.3%)	8 (17,8%)
3) Definitive CAN (score-2). Points 2 - 3	7 (23.3%)	13 (28,9)
4) Severe CAN (score-3). Points ≥ 3,5	3 (10%)	6 (13,3%)

Absence of CAN, according to proposed score, was defined in those patients without clinical features of cardiovascular problems. Near half of all patients (46,8%) presented with early and definitive CAN, while the higher prevalence of definitive CAN was shown in DM II patients. Severe CAN also was confirmed more often in DM II patients.

We analyzed and compared correlation between duration of DM and presence of CAN (see table 6).

Table 6: Relation between duration of disease and CAN in DM patients

DM history	CAN presence, No		CAN absence, No		Total, No	
	DM I	DM II	DM I	DM II	DM I	DM II
< 10 years	2 (11,8 %)	7 (25,9%)	9 (69,2%)	18 (100%)	11 (36,7%)	25 (55,6%)
> 10 years	13 (76,4%)	15 (55,6 %)	2 (15,4%)	0 (0%)	15 (50%)	15 (30%)
Firstly	2 (11,8%)	5 (18,5%)	2 (15,4%)	0 (0%)	4 (13,3%)	5 (11,1%)
Total	17	27	13	18	30	45

It was seen that history of DM I and DM II more than 10 years strongly correlated with high prevalence of CAN. But in cases of DM I 76,5% of patients suffering of disease longer than 10 years had clinically diagnosed CAN with only 11,8% of those with disease shorter than 10 years. Besides of patients with DM II, 55,6% of those who had CAN suffered of DM longer than 10 years, and 25,9% had this disease lesser than 10 years. All firstly diagnosed DM II patients were characterized with CAN presence, while half of the same DM I patients had not CAN in period of observation. Nobody of DM II patients with duration of disease longer than 10 years was free of CAN sings.

We analyzed and compared how the HbA1c level of DM patients can correlate with development of CAN (see table 7).

Table 7 : Glycemic control in DM patients depending of CAN presence

Type	Mean HbA1c of non-CAN patients, %	Mean HbA1c of CAN patients, %
DM I patients	11,17 ± 3,18	15,26 ± 2,54 *
DM II patients	8,23 ± 2,21	14,87 ± 4,34 *

Note: \* - significant difference ( $p \leq 0,05$ )

According to investigation, bad glycemic control increased risk of CAN development and stimulated its progression. On the other hand, glycemic control of DM I patients was worse than of DM II patients. We analyzed and compared how presence of sensory peripheral neuropathy in DM patients could correlate with development of CAN (see table 8).

Table 8: Sensory peripheral neuropathy among CAN patients

Type	CAN presence, No	Peripheral neuropathy presence, No	Peripheral neuropathy absence, No
DM I patients	17 (100%)	15 (88,2%)	2 (11,8%)
DM II patients	27 (100%)	19 (70,3%)	8 (29,7%)

Coexistence of CAN and peripheral neuropathy (sensory) was higher in patients with DM I than in DM II patients. Among DM I patients with CAN only 11,8% persons had not sensory peripheral neuropathy, while 29,7% DM II patients diagnosed CAN were free of sensory peripheral neuropathy.

We analyzed and compared how presenting of Diabetic retinopathy in DM patients could correlate with development of CAN (see table 9).

Table 9: Diabetic retinopathy and CAN

Type	Patients with diabetic retinopathy, No	Patients with diabetic retinopathy and CAN, No	Patients with diabetic retinopathy without CAN, No
DM I patients	12 (100%)	9 (75%)	3 (25%)
DM II patients	16 (100%)	11 (68,8%)	5 (31,2%)

It was revealed that co-presence of Diabetic retinopathy and CAN had developed more often in cases of DM I, 31,2% patients with DM II were suffering of Diabetic retinopathy without signs of CAN. 30% of all investigated DM I patients and 40,1% of DM II patients had combination of other diabetic complications with CAN. Frequency of that combination strongly correlated with duration of DM and level of glycemic control.

**CONCLUSIONS**

Thus, near 60% of investigated patients with DM type I and II were suffering from Cardiovascular Autonomic Neuropathy, affirming that CAN becomes a very common diabetic complication. Definitive and severe CAN were closer associated with DM II and can be explained by long undiagnosed period of disease in that patients. Development and progression of CAN were strongly correlated with prolongation of DM. All newly diagnosed DM II patients showed presence of CAN. Inadequate glycemic control in DM I patients directly corresponded to the development and progression of CAN. Association of the peripheral neuropathy, retinopathy and CAN was highly prevailed in DM I patients. CAN in investigated patients with DM I and II had developed primarily to peripheral neuropathy. So, careful and easy revealing of CAN by proposed standard tests could help in proper diagnoses of diabetic complications for the effective treatment and prevention of the adverse cardiovascular and cerebrovascular events in DM I and II patients.

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