ORIGINAL INVESTIGATION

Screening for cardiac autonomic neuropathy: preliminary results from Bosnia and Herzegovina

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Abstract

Introduction: Cardiac autonomic neuropathy (CAN) is important, but often neglected complication of diabetes, that substantially contributes to diabetes-related morbidity and mortality. The majority of diabetic patients have subclinical CAN. Therefore, screening for CAN in patients with diabetes is essential. The aim of this study was to assess the prevalence of subclinical CAN in real-life clinical setting at primary health care institution. We also aimed to determine, which routine clinical and laboratory parameters could serve as predictors of CAN.

Methods: We conducted a cross-sectional, prospective, observational study that included 50 consecutive patients with type 2 diabetes treated in the primary health care institution. Gender, age, duration of diabetes, glycated hemoglobin (HbA1c) levels, electrocardiogram, blood pressure, the presence of paresthesia, deep and superficial neuropathy, foot skin lesions and the presence of pulselessness of artery dorsalis pedis and tibialis posterior were recorded. The diagnosis of CAN was made if the patients met two out of three criteria: postural hypotension, increased resting heart rate and corrected QT interval prolongation.

Results: Patients had a median age of 59.0 (51.0 – 64.0) years and median duration of diabetes of 9.0 (6.0 – 11.0) years. CAN was present in 19 patients (38%). Patients with CAN had greater duration of diabetes and 2% higher HbA1c. They also had higher prevalence of peripheral neuropathy, foot skin lesions and peripheral artery disease. The presence of peripheral deep neuropathy was the best predictor of CAN with a specificity of 64.5% (45.4 - 80.8) and sensitivity of 79.0% (54.4 - 93.9).

Conclusion: CAN is a common complication in our cohort of patients with diabetes. Simple routine clinical and laboratory parameters may be useful in detecting patients at high risk for CAN.

Keywords: diabetes mellitus; cardiac autonomic neuropathy; peripheral neuropathy; screening; diabetic complications

1. Introduction

Diabetic neuropathy is the most common chronic complication of diabetes. Diabetic peripheral neuropathy is the most common cause of neuropathy, and therefore one of the most common acquired diseases of the nervous system. Two main types of diabetic neuropathy exist: peripheral and autonomic neuropathy. Peripheral neuropathy is categorized as typical and atypical and occurs as a result of deterioration of the peripheral nerves, due to prolonged exposure to hyperglycemia [1]. Autonomic diabetic neuropathy affects autonomic nervous system. It is characterized by spectrum of signs and symptoms, which affect the gastrointestinal, cardiovascular and urogenital system. Despite the fact that autonomic neuropathy substantially contributes to diabetes-related morbidity and mortally, is often neglected. The prevalence of autonomic nephropathy varies from 1% to 90% in patients with type 1 diabetes mellitus (T1DM) and 20% to 73% in patients with type 2 diabetes mellitus (T2DM). The main reason for such diversity of prevalence is due to the inconsistencies of criteria used for the it's diagnosis, but also due to great differences regarding the characteristics of studied population, in terms of age, gender and duration of diabetes [2]. After extensive analysis of the literature, the Consensus Panel on Diabetic Neuropathy has concluded and the prevalence of cardiac autonomic neuropathy (CAN) is approximately 20%, but can go up to 65% with increasing age and duration of diabetes [3]. According Subcommittee of the Toronto Consensus Panel on Diabetic Neuropathy, CAN was defined as an impairment of autonomic control of the cardiovascular system in patients with diabetes mellitus, after the exclusion of other causes [4]. CAN is a very common and often neglected complication of diabetes, which substantially contributes to the development of coronary heart disease and is a major risk factor for sudden cardiac death in patients with diabetes [5]. CAN is often present in patients with newly diagnosed T1DM and T2DM, suggesting that CAN may even occur before clinically evident diabetes [6]. However, duration of diabetes is an independent factor for CAN [4].

The pathogenesis of CAN is likely to be multi-factorial and to involve several mechanisms and pathways that lead to neuronal ischemia or direct neuronal death/dysfunction [7]. Hyperglycemia and adverse metabolic environment in patients with diabetes results in increased oxidative and nitrosative stress, which can cause direct neuronal damage, as well as endothelial dysfunction, resulting in neuronal ischemia and subsequent development of CAN [8]. Other mechanisms that contribute to the development of CAN, include autoimmune diseases, genetic predisposition and sleep apnea, while the residual pancreatic beta-cell function has a protective role [9-11]. CAN is divided into subclinical and clinical disease. Subclinical disease is characterized by denervation of parasympathetic nerves and consequent increase in sympathetic activity, which can be detected through abnormalities in heart rate, resting tachycardia and enhanced torsion of the left ventricle. Clinically evident CAN occurs after the denervation of the sympathetic nerves and presents mostly with postural hypotension [12].

Clinical manifestations of CAN include resting tachycardia, exercise intolerance, orthostatic hypotension, silent ischemia, diabetic cardiomyopathy, left ventricular dysfunction and sudden cardiac death. Orthostatic hypotension is defined as reduction in systolic blood pressure >20 mm Hg or diastolic blood pressure > 10 mmHg two minutes following postural change from supine to standing position. There are several diagnostic algorithms for the diagnosis of CAN. The majority of these algorithms include the presence of postural hypotension, heart rate abnormalities, heart rate response to deep breathing or Valsalva maneuver and measurement of the corrected QT inetrval (QTc). The presence of QTc prolongation alone can be used for the diagnosis of CAN with a reasonable specificity and sensitivity [13].

Screening for CAN in patients with diabetes is essential. According to numerous studies, the majority of diabetes patients with CAN have subclinical or asymptomatic disease, rendering the diagnosis of CAN in routine clinical practice difficult [12]. Moreover, diagnosing CAN at subclinical stage improves treatment and outcomes. The aim of this study was to assess the prevalence of subclinical CAN in real-life clinical setting at primary health care institution. We also aimed to determine, which routine clinical and laboratory parameters could serve as predictors of CAN.

2. Methods

This cross-sectional, prospective, observational study was conducted in the period March – April 2016 among patients with T2DM, treated in Department of Family medicine at the Healthcare Center in Gracanica, Bosnia and Herzegovina. A total of 50 consecutive patients were included in the study. Patients who met one or more of the following criteria were excluded from the study: diagnosis of carotid and brachial stenosis, the use of beta-blockers, diuretics and tricyclic antidepressants; and previously established diagnosis of peripheral neuropathy of different etiology. The following parameters were recorded and analyzed: gender, age, duration of diabetes, glycated hemoglobin (HbA1c) levels, electrocardiogram (ECG), resting heart rate, blood pressure, the presence of paresthesia, deep and superficial neuropathy, foot skin lesions and the presence of pulselessness of artery dorsalis pedis (ADP) and tibialis posterior (ATP).

All parameters were recorded in the mornig after an overnight fasting. Patients were asked to avoid consuming cigarettes, coffee or black tea before the examination. Blood pressure was measured on both hands, while sitting and then after 2 minutes of standing. The postural fall after 2 min in blood pressure was calculated as the difference between systolic blood pressure sitting and the systolic blood pressure standing. Postural hypotension was defined as postural fall in systolic blood pressure >20 mm Hg or diastolic blood pressure > 10 mmHg. ECG was recorded after lying for at least 10 minutes. Increased heart rate was defined as heart rate > 100 beats/min. QTc interval prolongation was defined as QTc above 450 ms in males and above 470 ms for females, after performing correction for heart rate. The diagnosis of CAN was made if the patients met two out of three criteria: postural hypotension, increased resting heart rate and QTc prolongation.

2.1. Statistical analyses

Continuous variables were compared with Mann-Whitney test and expressed as median with interquartile range. Categorical variables with Fisher exact test. Spearman correlation was performed in order to analyze the association between the variables. Receiver operating characteristic (ROC) analysis was performed

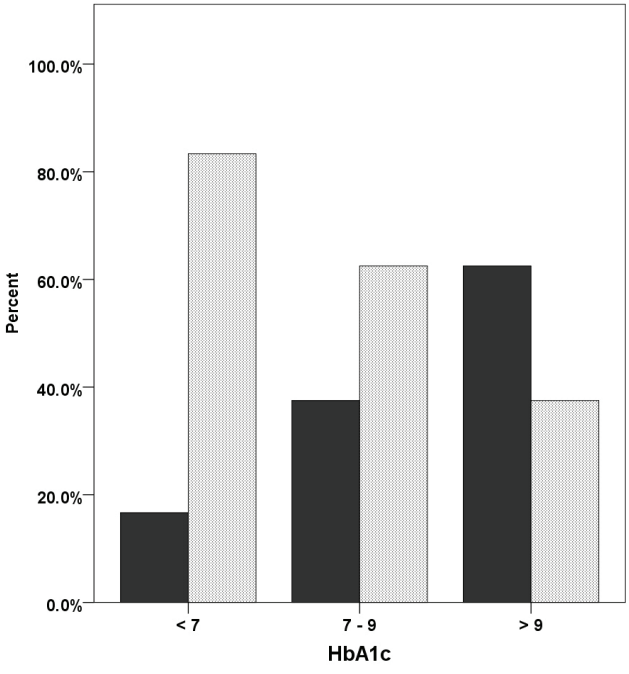

Figure 1. The presence of CAN (black bars) in patients divided based on their HbA1c levels.

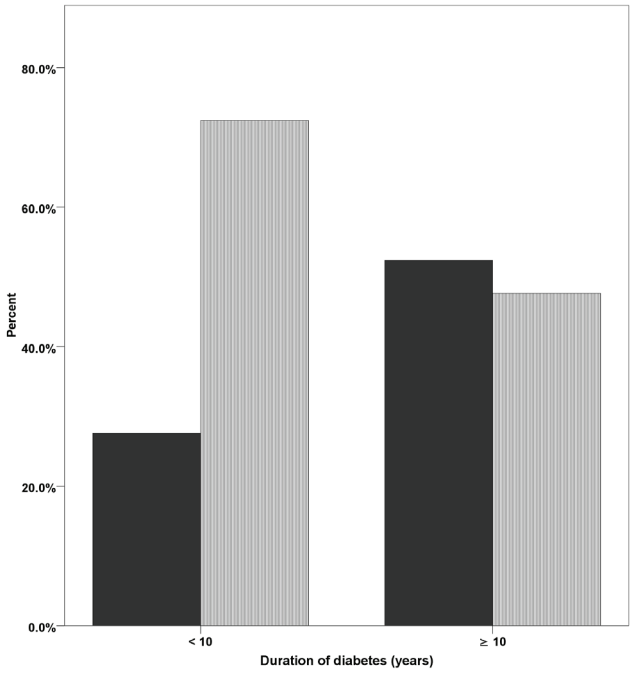

Figure 2. The presence of CAN (black bars) in patients divided based on the duration of diabetes.

to establish optimal cut-off values for continuous variables and to calculate sensitivity and specificity. ROC analysis was performed only for variables with significant Spearman correlation coefficients. Statistical analyses were performed in SPSS version 20.0. P values < 0.05 were considered statistically significant.

3. Results

Patients had a median age of 59.0 (51.0 – 64.0) years and median duration of diabetes of 9.0 (6.0 – 11.0) years. There were 32 females (64%) and CAN was present in 19 patients (38%). Age was inversely associated with QT prolongation (ρ = -0.291, P = 0.041), while there were no significant association between gender and other parameters. Patients with CAN had greater duration of diabetes and higher HbA1c levels (Table 1, Figures 1 and 2). They also had higher prevalence of peripheral neuropathy, skin lesions and peripheral artery disease. Postural hypotension was present in all patients with CAN, while approximately two thirds of patients with CAN had QT interval prolongation and increased resting heart rate (Table 1). The presence of CAN correlated positively with duration of diabetes, HbA1c, peripheral neuropathy and artery disease, but deep peripheral neuropathy correlated best with the presence of CAN (Table 2). Each of these parameters had approximately 70% diagnostic accuracy in predicting CAN. We designed a scoring system in which each of these variables were stated 0 (absent) or 1 if the parameter was present. However, the scoring system did not increase the diagnostic accuracy (Table 3).

Table 1. Study population divided based on the presence of cardiac autonomic neuropathy

	CAN present N=19	CAN absent N=31
Age (years)	59.0 (56.0 – 71.0)	59.0 (49.0 - 64.0)
HbA1c (%)	9.1 (8.1 - 11.8) †	7.1 (6.3 - 8.7)
Duration of diabetes (years)	10.0 (7.0 - 12.0) †	8.0 (5.0 - 10.0)
Female gender %(n)	73.7 (14)	58.1 (18)
Deep neuropathy %(n)	78.9 (15) †	35.5 (11)
Superficial neuropathy %(n)	84.2 (16) †	41.9 (13)
Skin lesions %(n)	63.2 (12) †	19.4 (6)
Paresthesia %(n)	78.9 (15) †	41.9 (13)
Pulselessness ATP %(n)	63.2 (12)	35.5 (11)
Pulselessness ADP %(n)	57.9 (11) †	29.0 (9)
Postural hypotension %(n)	100.0 (19) †	32.3 (10)
QT prolongation %(n)	52.6 (10) †	0.0 (0)
Increased heart rate %(n)	68.4 (13) †	0.0 (0)

† P<0.05

Table 2. Correlation coefficients (rho) and P values showing the strength of Spaerman correlation between each parameter and the presence of CAN

	Duration of DM	HbA1c	Deep neuropathy	Superficial neuropathy	Diabetic foot	Paresthesia	Pulselessness ATP	Pulselessness ADP
Postural hypotension	.559 .000	.561 .000	.805 .000	.507 .000	.638 .000	.552 .000	.541 .000	.529 .000
QT prolongation	.293 .039	.317 .025	.380 .006	.324 .022	.458 .001	.342 .015	.241 .092	.408 .003
Heart rate	.126 .385	.387 .005	.296 .037	.320 .024	.315 .026	.250 .080	.185 .199	.074 .607
CAD score	.467 .001	.568 .000	.694 .000	.518 .000	.630 .000	.521 .000	.457 .001	.465 .001

Table 3. Sensitivity and specificity of each variable and combination of all variables (score) in predicting CAN.

	Specificity	95% CI	Sensitivity	95% CI
HbA1c > 6.6	48.39	30.2 - 66.9	94.74	74.0 - 99.9
Skin lesions	80.65	62.5 - 92.5	63.16	38.4 - 83.7
Paresthesia	58.06	39.1 - 75.5	78.95	54.4 - 93.9
Deep sensor loss	64.52	45.4 - 80.8	78.95	54.4 - 93.9
Superfitial sensor loss	58.06	39.1 - 75.5	84.21	60.4 - 96.6
Score > 3	64.52	45.4 - 80.8	78.95	54.4 - 93.9

4. Discussion

CAN is one of the most important, but usually overlooked complication of diabetes, that affects equally patients with T1DM and T2DM. CAN is associated with a poor prognosis and a poor quality of life [14]. It can lead to severe or even fatal acute myocardial infarction by causing silent ischemia. Prolonged QTc can cause serious cardiac arrhythmias, ventricular tachycardia or fibrillation. Consequent development of cardiomyopathy and left ventricular leads to decreased quality of life. Cardiovascular adverse events are approximately three times more common in patients with diabetes compared with patients without diabetes [15]. Therefore, CAN is closely associated with fatal outcomes of cardiovascular disease as well as with other causes of mortality of patients with CAN [16]. A meta-analysis showed that CAN-related abnormalities in heart rate strongly correlated with increased risk of silent myocardial ischemia and mortality [17]. The majority of diabetes complications can be prevented with good glycemic control, although some complications can develop despite the good glycemic control. The role of strict glucose control in slowing the progression of CAN is still debated. Although, several studies have showed that poor blood glucose control plays an important role in the development and progression of CAN [14,18], large longitudinal study reported that

the development of cardiovascular autonomic dysfunction was independently associated with microvascular complications and glycemic control status during 7.5-year follow-up in patients with T2DM [19]. Our study showed that the patients with poor glycemic control had higher prevalence of CAN. Patients with HbA1c < 7% had a prevalence of CAN of 17%. CAN prevalence tripled in the group of patients with HbA1c > 9%. In the group of patients with a history of diabetes longer than 10 years, the prevalence of CAN was 2-fold higher when compared with a group of patients with a history of diabetes shorter than 10 years. In a study conducted by Pappachan JM at all, 60% of patients with diabetes suffered CAN. Statistical analysis showed a significant association between CAN and age, prolonged QTc and duration of diabetes [13], which is similar to our results.

CAN progression from subclinical to clinically manifest stage is unclear, but symptoms usually develop within five years from the occurrence of abnormalities in heart rate. Since CAN has an impact on the development of silent myocardial ischemia, dysfunction of the left ventricle and fatal arrhythmias, early diagnosis of CAN very important. CAN treatment can be either symptomatic or directed towards the slowing of CAN progression. However, the efficacy of all treatment options is modest. Based on our current understanding of CAN pathogenesis and risk factors, several potential treatments have been studied. Lifestyle modification can have benefits in preventing and slowing the progression of CAN. Lifestyle modifications include behavioral therapy (diet, physical exercise, smoking cessation) and pharmacological therapy for important comorbidities, such as hypertension and hyperlipoproteinemia. In the Steno-2 study, which included patients with T2DM, the prevalence of CAN was significantly lower in the group with lifestyle modification than in the control group after 7.8 years of follow-up (49% vs 65%) [20,21].

Previous studies have showed that CAN often coexists with other complications of diabetes, mostly peripheral neuropathy. Prevalence rates of pure autonomic and of pure peripheral neuropathy in patients with T2DM are approximately 20% [22]. Thus, the vast majority of patients with CAN have signs and symptoms of peripheral neuropathy. Our study is first to show that these clinical signs and symptoms may be used to detect patients with CAN. The presence of peripheral deep neuropathy showed 75% diagnostic accuracy in predicting CAN. Therefore, we suggest that screening for can should be mandatory for patients with peripheral neuropathy.

Treatment options that would affect the pathogenesis of CAN are limited. However, using the alpha-lipoic acid showed to improve CAN in patients with T2DM [23]. In patients with chronic heart failure and CAN, bisoprolol showed beneficial effects on autonomic function [24]. Angiotensin receptor blockers showed also some beneficial effects on parasympathetic / sympathetic balance [25]. Treatment of postural hypotension is required for symptomatic patients. There are several strategies available including lifestyle and behavior of the measures, as well as pharmacological treatment. Patients should be advised to avoid sudden changes in posture, frequent and smaller meals and to avoid drugs that cause postural hypotension (diuretics, tricyclic antidepressants, alpha agonists adrenaline receptors) [26].

5. Conclusions

CAN is a common and underdiagnosed complication of T2DM in Bosnia and Herzegovina. CAN is associated with a significant increase in morbidity and mortality, and plays a very important role in the development of diabetic cardiomyopathy and silent ischemia. CAN prevalence correlated positively with the duration of diabetes, HbA1c levels, the presence of peripheral neuropathy, foot skin lesions and peripheral artery disease. Simple routine clinical and laboratory parameters may be useful in detecting patients at high risk for CAN.

Author contributions

BA and SA gave the idea for the article, wrote the paper, participated in drafting the article, performed literature review and gave their the final approval. AJ and CM participated in data collection, drafting of article and gave their final approve. SS performed statistical analyses and gave final approval. PF and BM critically revised the manuscript, gave suggestions regarding data presentation and gave their final approval.

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