REVIEW ARTICLE

Diabetic cardiovascular autonomic neuropathy: A review

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RESUMEN

La neuropatía diabética se considera una complicación microvascular de la diabetes mellitus. Se clasifica como focal o difusa, y dependiendo del tipo de fibras afectadas y su localización se subclasifica como de vías periféricas autónomas, sensitivas o motoras. La neuropatía diabética autonómica (DAN), particularmente la de tipo cardiovascular, se asocia a una mayor mortalidad y morbilidad, sobre todo en pacientes con diabetes de larga evolución y descontrol glucémico crónico. Los principales factores predictores de desarrollo de neuropatía autonómica cardiovascular (CAN) en pacientes con diabetes mellitus tipo 2 (DM2) son la edad, género, etnia y la presencia de otras complicaciones microvasculares. Sus manifestaciones clínicas incluyen taquicardia en reposo, intolerancia al ejercicio, hipotensión ortostática, isquemia silente y cardiomiopatía diabética. Desafortunadamente no existe un tratamiento específico de la DAN. Los pilares del tratamiento son la prevención y la detección temprana. Esta revisión incluye la epidemiología, fisiopatología, presentación clínica y pruebas diagnósticas y tratamiento de CAN.

Palabras clave. Neuropatía autonómica diabética. Enfermedades autonómicas. Diabetes mellitus. Complicaciones de diabetes mellitus.

ABSTRACT

Diabetic neuropathy is one of the microvascular complication of diabetes mellitus. It is classified, as focal or diffuse, and according to the nervous fiber type and its localization, it is classified in to peripheral, autonomic, sensitive or motor neuropathy. Diabetic autonomic neuropathy (DAN) is associated with an increased morbidity and mortality particularly in patients with longstanding-poor controlled diabetes. The main predictors of development of cardiovascular autonomic neuropathy (CAN) in patients with type 2 diabetes are age, gender, ethnicity and presence of other microvascular complications. The main clinical manifestations presented in CAN patients are resting tachycardia, exercise intolerance, orthostatic hypotension, silent ischemia and diabetic cardiomyopathy. Unfortunately, there is no specific treatment of DAN. The mainstay of treatment for this disease is prevention and early detection. This review focuses on epidemiology, physiopathology, clinical manifestations, diagnostic studies and treatment of CAN.

Key words. Diabetic neuropathies. Autonomic nervous system diseases. Diabetes complications.

INTRODUCTION

Diabetic neuropathy (DN) is the leading cause of neuropathy in the world. It is characterized by damage to peripheral nerves (sensory, motor and autonomic) because of increased glucose in serum and tissues.[1] Diabetic autonomic neuropathy is a common form of DN, which is associated with increased morbidity and mortality, especially in patients with longstanding-poor controlled diabetes.[1,2] DAN is asymptomatic in the early stages, thus detection and diagnosis are difficult.[1]

DEFINITION

Diabetic neuropathy (DN) is defined as the presence of signs or symptoms of peripheral nerve dysfunction (sen-

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sorial, motor and autonomic nerves) in people with diabetes, in whom other nerve dysfunction causes have been excluded.[1]

Thomas & Boulton classified DN in three groups: Generalized symmetrical polyneuropathy (GSP), focal and multifocal neuropathy. With a prevalence of 30-45%, the most common types of GSP are sensitive peripheral neuropathy (SPN) and autonomic neuropathy (DAN).[1] DAN affects cardiovascular (CAN), cerebrovascular, gastrointestinal, genitourinary and sexual systems. Because of its clinical importance, CAN is the most studied variant.[1]

The Toronto Consensus Panel for Diabetic Autonomic Neuropathy defined CAN as an altered autonomic control of the cardiovascular system in patients with established diagnosis of diabetes mellitus, in whom other nerve dysfunction causes had been excluded.[2,3] It is associated with a wide variety of manifestations such as exercise intolerance, perioperative cardiovascular disorders, orthostatic syndromes, arrhythmias and silent myocardial ischemia. These manifestations and its outcomes have critical importance as they can endanger life in this population.[2]

EPIDEMIOLOGY

Diabetes mellitus (DM) affects at least 8.3% of the world population. It is estimated that 1 in 6 people with diabetes are at risk of developing complications associated with this disease.[2]

CAN prevalence ranges from as low as 1% to as high as 90% in longstanding DM as Pop Busui, *et al*. (2009)[4] and Verrotti, *et al*. (2014)[1] have described. When differentiation is made according to diabetes mellitus type, Dimitropoulos, *et al*. reported a prevalence ranging from 1 to 90% in patients with DM type 1 (DM1) and 20 to 70% in patients with DM type 2 (DM2).[3] In a population-based study, the prevalence of autonomic neuropathy, defined by an alteration in one or more tests to identify heart rate variability (HRV) was 16.7%.[5] This percentage discrepancy in prevalence can be understood because of the heterogeneity of the patients and on the lack of a universal diagnostic criterion for CAN.

CAN is found in 7% of patients with DM1 and DM2 at diagnosis[3,8] and it is estimated that the annual risk of developing CAN is 6% for patients with DM1 and 2% for patients with DM2.[3] Prevalence increases with age and years of evolution of DM, going up to 65% for older patients.[6,7] In the age group from 40 to 70 years with DM1 numbers go from 38 to 44% and in DM2 35 to 65% in patients with longstanding diabetes.[8]

When other macrovascular complications are associated to DAN, an association has been found. A meta-analysis by Vinik, *et al*. included 12 studies. He identified a consistent association between CAN and silent myocardial ischemia.[9] The detection of silent myocardial ischemia in asymptomatic diabetic subjects (DIAD study) found that CAN in DM2 was a strong predictor of silent ischemia and subsequent cardiac events.[10] Also, The Action to Control Cardiovascular Risk in Diabetes (ACCORD study group) patients who were diagnosed with CAN had 2-fold increase in risk of death compared to those without this diagnosis.[11]

CAN has also been associated with an increased risk of sudden cardiac death,[13,14] which can be explained by the increase in the rate of fatal cardiac arrhythmias secondary to an imbalance between sympathetic and parasympathetic autonomic function.[15]

RISK FACTORS

The main predictors for the development of CAN in patients in DM2 are age, gender, ethnicity and presence of microvascular complications (nephropathy, retinopathy, and peripheral neuropathy).[3]

In a cohort of 1,000 patients with DM2, the incidence of CAN 7.5 years of follow-up was correlated with older age ($p < 0.001$) and the presence of microvascular disease ($p = 0.035$)[16] (Table 1).

In terms of gender, in a multicenter study of 3,250 patients with DM, there was no difference in the prevalence of CAN between men and women (men 35% and women 37%).[17] However, The ACCORD study which involved more than 8000 DM2 patients, CAN was more prevalent in women (2.6% in men and 4.7% in women for moderate to severe and 1.4% in men and 2.2% in women for severe).[12]

PATHOGENESIS

The pathogenesis of diabetic autonomic neuropathy involves a cascade of pathways activated by hyperglycemia, resulting in ischemia and neuronal dysfunction or cell death.[1,3]

Table 1. Risk factors for autonomic neuropathy in diabetes mellitus.

• Older age.
• Female gender.
• European ethnicity.
• Microvascular complications (nephropathy and peripheral mono or poli-neuropathy).

The increase in serum glucose and intracytoplasmic overproduction of reactive oxygen species and nitrogen (ROSN) such as superoxide radicals, hydrogen peroxide and peroxynitrite. The ROSN induced DNA damage results in endothelial dysregulation, triggering of pro-apoptotic signaling and the formation of advanced glycation end products (AGEs). AGEs interact with specific surface receptors (RGEPs), creating a complex pro-inflammatory cascade (IL-1, IL-6, TNF-α, TGF-β, VCAM-1) and increased oxidative stress.[18]

Cellular damage is produced by ROSN, by protein kinase C (PKC) pathway activation and hexosamine mediated by NADPH oxidase complex. Moreover, excessive tissue and intracellular glucose increase the production of polyols, especially sorbitol, which in turns increases NAPH consumption and lack of this important antioxidant in the cellular regeneration process.[19]

The phenomenon described produces a state of chronic inflammation in which the expression of adhesion molecules, cytokine overproduction, infiltration of phagocytic cells and activation of the innate immune system by means of Toll like receptors (TLR-2 and TLR-4) participate in secondary neuronal and vascular damage.[20].

Moreover, tissue glucose increases microvascular injury produced by different mechanisms, including increased production of tissue plasminogen activator inhibitor-1 and endothelin-1.[3]

CLINICAL MANIFESTATIONS

Chronic hyperglycemia promotes progressive autonomic neural dysfunction affecting the autonomic nervous system in an ascending order, beginning distally and progressing proximally. Because neuropathy is observed first in the longest fibers, the earliest manifestations are parasympathetic, for example, the long fibers of the vagus nerve, which controls 75% of the parasympathetic activity.[3] Later, DAN is characterized by sympathetic denervation, affecting the heart from the apex to the base, gradually altering ventricular contractility and causing cardiomyopathy. At this stage, autonomic dysfunction clinically correlates with postural hypotension.[1,3,21]

Before being clinically evident, CAN presents with a subclinical phase manifested by decreased heart rate variability due to parasympathetic denervation.[3] In a more advanced stage, DAN is characterized by sympathetic denervation, affecting the heart from the apex to the base, gradually altering the ventricular contractility and causing cardiomyopathy. At this stage, autonomic dysfunction clinically correlates with postural hypotension.[1,3,21]

Table 2. Clinical manifestations of diabetic autonomic neuropathy.

- Subclinical phase.
  Decreased heart rates variability.
- Early phase.
  Resting tachycardia.
- Advanced stage.
  Excercise intolerance.
  Cardiomyopathy with left ventricular dysfunction.
  Postural hypotension.
  Silent cardiac ischaemia.

The main clinical manifestations of CAN are: Resting tachycardia, exercise intolerance, orthostatic hypotension, silent ischemia and diabetic cardiomyopathy with left ventricular dysfunction[3] (Table 2).

In resting tachycardia, heart rates between 90 to 130 beats per minute are observed at rest. Heart rate that does not change during sleep, exercise or stress is a sign of complete cardiac denervation.[3,22]

Impairment of exercise tolerance refers to changes in blood pressure, heart rate, and cardiac stroke volume in response to exercise, in the absence of structural or coronary heart disease.[3]

Orthostatic hypotension is an advanced manifestation of CAN. It is defined as a reduction in systolic blood pressure > 20 mmHg or diastolic blood pressure > 10 mmHg within two minutes after changing from supine to seated position. Orthostatic hypotension is due to an inappropriate sympathetic response to a postural change, which is secondary to a low norepinephrine response and an abnormal sensitivity baroreceptor, resulting in an inadequate response of the heart rate and peripheral vasoconstriction.[22,23]

Silent ischemia refers to CAN patients who have a subjective high threshold to develop angina, meaning a larger time between the observation of a 1 mm ST electrocardiogram depression and the development of the first symptoms of angina. It represents a higher risk for silent ischemia and infarction, despite being asymptomatic.[3]

Diabetic cardiomyopathy results in different degrees of systolic dysfunction, but predominantly diastolic in the absence of structural or valvular heart disease, coronary artery disease or hypertension. Often the only detectable abnormality in early stages of CAN, is an isolated diastolic dysfunction with an ejection fraction of the normal left ventricle, associated with high cardiovascular morbidity.[3]

DIAGNOSIS

There is no diagnostic test for CAN that is widely accepted as a gold standard. In 1982, Ewing and Clarke[24,25] proposed a battery of non-invasive diagnostic tests to measure autonomic cardiac function. They took into account the RR interval and blood pressure changes to certain physiological maneuvers.[26]

Ewing described 5 maneuvers during the test, three of them evaluates difference in the RR interval and two of them identify differences in systolic and diastolic blood pressure:[35]

- Heart rate response is measured against deep breaths for 2 min, at 6 breaths per minute (5 sec in and 5 sec out for 1 min). An electrocardiogram is recorded throughout the period of deep breathing, with a marker used to indicate the onset of each inspiration and expiration. The maximum and minimum R-R intervals in each cycle are measured with a ruler and converted to beats a minute. Result is expressed as the mean of the difference between maximum and minimum heart rates for the six measured cycles in beats a minute.
- Immediate heart-rate response to standing (also known as the ratio 30:15). It is performed with the patient lying on a couch while the heart rate is recorded continuously on an electrocardiograph. The patient is then asked to stand up unaided. The point at starting to stand is marked on the electrocardiogram. The ratio 30:15 is the ratio between the longest R-R interval (between 20 and 40 beats) and the shortest R-R interval is measured (between heart beat 5-25). People with DAN show only a gradual or no increase in heart rate after standing.
- The heart rate response to the Valsalva maneuver is measured during and after an increase in intra thoracic and intra-abdominal pressure (the patient breathes normally by a 15 sec period with a fixed resistance). Normally during Valsalva maneuver, the blood pressure drops and the heart rate rises. In patients with DAN, blood pressure slowly falls during strain and slowly returns to normal after release, with no overshoot rise in blood pressure and no change in heart rate.
- Blood-pressure response to standing. On standing, pooling of blood in the legs causes a fall in blood pressure, which is rapidly corrected by peripheral blood vessel constriction. In patients with DAN, the blood pressure falls on standing and remains lower than the lying position.
- Maximal response of diastolic blood pressure to sustained muscle contraction using a dynamometer (blood-pressure response to sustained handgrip). During sustained handgrip a sharp rise in blood pressure occurs, due to a heart-rate-dependent increase in cardiac output with unchanged peripheral vascular resistance. In patients with DAN normal reflex pathways are damaged, in then, the rise in blood pressure is abnormally small (handgrip is maintained at 30% of the maximum for as long as 5 min). Blood pressure is measured three times before and at one-minute intervals during handgrip. Results are expressed as the difference between the highest diastolic blood pressure during handgrip exercise and the mean of the three diastolic blood-pressure readings before the handgrip began.

According to CAN subcommittee in the Toronto Diabetic Neuropathy Consensus Panel, conducted in 2010, CAN diagnostic criteria are divided as follows: A positive test is early diagnosis of CAN; the presence of two or three positive tests is required for definitive diagnosis of CAN; the presence of orthostatic hypotension combined with one of the previous criteria is defined as advanced or severe CAN.[27]

Proof of Ewing is a set of noninvasive studies for diagnosis of CAN, which although is not a gold standard for diagnosis, is the most widely accepted test, as it has a sensitivity of 87.3% and specificity of 80.46%.[28]

The expert group of diabetic neuropathy Toronto, recommends that CAN screening should be considered in patients with type 2 diabetes at the time of diagnosis and after 5 years of diagnosis in patients with type 1 diabetes, especially in patients with other micro or macrovascular complications.[29] Patients with a history of poor glycemic control (HbA1c > 7%) are those who are at increased risk of CAN, so that this group of patients benefits from screening for CAN.[3,27]

Evidence also suggests that CAN screening should be included in the preoperative evaluation of patients with poor glycemic control and coronary artery disease because of a known association between CAN and perioperative hemodynamic instability.[30]

PREVENTION AND TREATMENT

There is no specific treatment for DAN. The mainstay of treatment of this disease is prevention and early detection.

In the Steno-2 study in patients with type 2 diabetes and microalbuminuria, intensive medical intervention to achieve blood pressure, microalbuminuria, lipid goals plus lifestyle changes, reduced the risk to develop CAN, when

followed for 7.8 years. This study also showed a reduction in cardiovascular disease and mortality.[3,31]

The Program for the Prevention of Diabetes (PPD) showed that changes in lifestyle, especially weight loss and increased physical activity, did improve indices of autonomic function (HRV and QT interval) rather than metformin or placebo.[31] A review published in 2007 also exhibited better in autonomic function in patients with diabetes and obesity post-significant weight loss.[32]

As for treatment, studies in a systematic review by Callaghan, *et al*., in 2012, indicated that intensive insulin therapy decreases progression of peripheral neuropathy and CAN in patients with type 1 diabetes.[33] In patients with type 2 diabetes, intensive glycemic control has not shown significant differences in the incidence of CAN;[34] however, in this group of patients, various hypoglycemic agents such as sulfonylureas, GLP-1 agonist and thiazolidinediones, have revealed beneficial effects around macrovascular diabetic complications,[35] specifically GLP-1 agonists and inhibitors of DPP-4 have shown neuroprotective and cardio protective effects.[36]

Evidence suggests that the use of alternative treatments, such as vitamin E and C-peptide may be useful in the management of DAN.[27,37] Studies are underway to identify the role of inhibitors of antioxidant pathways, especially NF-κB and Nfr-2, as future strategies for the management of DAN1. Further studies are needed to confirm the effectiveness of alternative treatments for DAN.

CONCLUSIONS

Diabetic autonomic neuropathy is associated with increased morbidity and mortality, particularly in patients with longstanding and poor control of diabetes. After reviewing the issue in depth of cardiovascular autonomic neuropathy, given its clinical significance, it has been the most studied but lacks implement screening protocols for diagnosis and treatment. Since there is no gold standard for the diagnosis, we propose Ewing testing in newly diagnosed diabetic patients in order to avoid long-term complications, especially in patients with a history of poor glycemic control, since there is not a specific treatment, the best way to prevent this disease is through prevention and early detection.

HIGLIGHTS

- Cardiovascular diabetic autonomic neuropathy is associated with increased morbidity and mortality.
- Predictors of cardiovascular autonomic neuropathy development are age, gender, ethnicity and presence of other microvascular complications.
- Clinical manifestations include resting tachycardia, exercise intolerance, orthostatic hypotension, silent ischemia and diabetic cardiomyopathy.
- There is no specific treatment for diabetic autonomic neuropathy.

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