



## **Cardiovascular Autonomic Neuropathy in Type 2 Diabetic Patients with No Obvious Clinical Disease: Review article**

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**Abstract:** Diabetic autonomic neuropathy (DAN) is among the least recognized and understood complications of diabetes despite its significant negative impact on survival and quality of life in people with diabetes. Cardiovascular autonomic neuropathy (CAN) is the most clinically important and well-studied form of diabetic neuropathy and was detected by standard autonomic reflex tests. In its course, it can result in a variety of symptoms and signs like resting tachycardia, exercise intolerance, orthostatic hypotension, decreased heart rate variability (HRV), diabetic cardiomyopathy and silent myocardial ischemia. Identifying individuals at risk is only the first step in managing patients and ultimately affecting outcomes. After identification, effective management must be provided. Unfortunately, it is often recognized too late and then it can have serious consequences for patient health and even life. With the help of simple autonomic tests, CAN can be diagnosed already in the asymptomatic phase. Strict blood glucose control is still the only causal therapy aimed at preventing, halting or slowing its progression.

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### **Introduction:**

The prevalence of diabetes mellitus (DM) has risen in recent decades, and cardiovascular disease remains the leading cause of death in this population. Several clinical trials have demonstrated the benefit of tight control of risk factors on the incidence and mortality of cardiovascular disease. However, in clinical practice, few patients achieve the therapeutic goals. The current diagnostic procedures for subclinical disease in diabetic patients have been shown to improve prognosis and prevent development of overt clinical diseases. (1)

Diabetic autonomic neuropathy (DAN) is among the least recognized and understood complications of diabetes despite its significant negative impact on survival and quality of life in people with diabetes. (2, 3)

Cardiovascular autonomic neuropathy (CAN) is the most clinically important and well-studied form of diabetic neuropathy and was detected by standard autonomic reflex tests. In its course, it can result in a variety of symptoms and signs like resting tachycardia, exercise intolerance, orthostatic hypotension, decreased heart rate variability (HRV), diabetic cardiomyopathy and silent myocardial ischemia. Unfortunately, it is often recognized too late and then it can have serious consequences for patient health and even life. With the help of simple

autonomic tests, CAN can be diagnosed already in the asymptomatic phase. Strict blood glucose control is still the only causal therapy aimed at preventing, halting or slowing its progression. (5)

The prevalence of CAN varies from 20% to 73% in patients with type 2 diabetes and from 1% to 90% in patients with type 1 diabetes. The importance of this diabetic complication is best illustrated by the fact that the mortality rate in patients with CAN is 5-6 times higher in the period of 5-6 years than the mortality in patients with diabetes but without CAN in the same period. (6)

The increased mortality found for patients with clinical symptoms of autonomic neuropathy were due to both a direct effect of the autonomic neuropathy itself and an indirect, but parallel, association with accelerating microvascular complications. (7)

### **Clinical Presentation of CAN:**

In this report, the clinical manifestations (e.g., exercise intolerance, intraoperative cardiovascular lability, orthostatic hypotension, and increased risk of mortality) of the presence of CAN will be discussed. It will also be shown that autonomic dysfunction can affect daily activities of individuals with diabetes and may invoke potentially life-threatening outcomes. Advances in technology, built on decades of research and clinical testing, now make it possible to objectively identify early stages of CAN with the use

of careful measurement of autonomic function.

**Exercise intolerance:**

Autonomic dysfunction can impair exercise tolerance (8). In a study of individuals with and without CAN, Kahn et al. showed a reduced response in heart rate and blood pressure during exercise in individuals with CAN. (9) Roy et al. demonstrated a decreased cardiac output in response to exercise in individuals with CAN. (10)

**Intraoperative cardiovascular lability:**

Hemodynamic changes occur during surgery for individuals with and without diabetes. Burgos et al. found that vasopressor support was needed more often in diabetic individuals with autonomic dysfunction than in those without. (11)

**Orthostatic hypotension:**

Orthostatic hypotension is defined as a fall in blood pressure (i.e., <20 mmHg for systolic or <10 mmHg for diastolic blood pressure) in response to postural change, from supine to standing (12).

In patients with diabetes, orthostatic hypotension is usually due to damage to the efferent sympathetic vasomotor fibers, particularly in the splanchnic vasculature (13). In addition, there is a decrease in cutaneous, splanchnic and total vascular resistance that occurs in the pathogenesis of this disorder. Normally, in response to postural change there is an increase in plasma norepinephrine. For individuals with orthostatic hypotension, there may be a reduction in this response relative to the fall in blood pressure (14).

**Silent myocardial ischemia/cardiac denervation syndrome:**

The cause of silent myocardial ischemia in diabetic patients is controversial. It is clear, however, that a reduced appreciation for ischemic pain can impair timely recognition of myocardial ischemia or infarction and thereby delay appropriate therapy. This agrees with the results of 12 cross-sectional studies, comparing the presence of silent myocardial ischemia, generally measured by exercise stress testing between diabetic individuals with and without CAN. Of the

12 studies, 5 showed a statistically significant increased frequency of silent myocardial ischemia in individuals with CAN compared with individuals without CAN. The point estimates for the prevalence rate ratios in these 12 studies ranged from 0.85 to 15.53. The prevalence rate ratio was <1 in 10 of the 12 studies, and in 4 of these, the lower limit of the 95% CI was <1. Via meta-analysis, the Mantel-Haenszel estimate for the pooled prevalence rate risk for silent myocardial ischemia was 1.96, with a 95% CI of 1.53–2.51 (P 0.001; n 1,468 total subjects).

(15-17)

**Increased risk of mortality:**

Many previous studies had investigated and examined the association of autonomic dysfunction

and mortality. These studies have consistently provided evidence for an increased mortality risk among diabetic individuals with CAN compared with individuals without CAN.

**Association of CAN with major cardiovascular events:**

The relationship between CAN and major cardiovascular events has been assessed in two prospective studies. Specifically, the relationship between baseline CAN and the subsequent incidence of a fatal or nonfatal cardiovascular event, defined as an MI, heart failure, resuscitation from ventricular tachycardia or fibrillation, angina, or the need for coronary revascularization, was examined. The relative risks associated with CAN in these studies were 2.2 and 3.4, respectively, with the latter result just achieving statistical significance (P 0.05). It would appear, therefore, that there is an association between CAN and major cardiovascular events, but given the small number of events that occurred in each of these studies, more follow-up studies are required. (18).

**CAN and sudden death:**

A number of researchers have reported sudden unexpected deaths among subjects identified with autonomic neuropathy. One potential cause of sudden death may be explained by severe but asymptomatic ischemia, eventually inducing lethal arrhythmias (19).

An autonomic imbalance resulting in QT prolongation may also predispose individuals to life-threatening cardiac arrhythmias and sudden death. Results from the EURODIAB IDDM Complications Study showed that male patients with impaired HRV had a higher corrected QT prolongation than males without this complication (20).

**Increased mortality after an MI:**

Mortality rates after an MI are also higher for diabetic patients than for non-diabetic patients. This may be due to autonomic insufficiency, increasing the tendency for development of ventricular arrhythmia and cardiovascular events after infarction. (21)

**Association of CAN with cerebrovascular disease:**

The frequency of ischemic cerebrovascular events is increased in individuals with type 2 diabetes. The impact of autonomic dysfunction on the risk of the development of strokes was examined by Toyry et al., who followed a group of 133 type 2 diabetic patients for 10 years. During the study period, 19 individuals had one or more strokes. Abnormalities of parasympathetic and sympathetic autonomic function were found to be independent predictors of stroke in this cohort (22).

**Diagnosis of CAN:**

A large body of evidence indicates that these factors can, to various degrees, affect the cardiovascular ANS and potentially other autonomic organ systems (23). Heart rate response to deep

breathing is for the most part a function of parasympathetic activity, although the sympathetic nervous system may affect this measure (24). Similarly, it is parasympathetic activity that plays the greatest role in the heart rate regulation for short-term standing, where the act of standing involves low-level exercise and parasympathetic tone is withdrawn to produce a sudden tachycardic response (25).

In response to subsequent underlying blood pressure changes while standing, a baroreceptor-mediated reflex involves the sympathetic nerves for further heart rate control. Measurements of blood pressure response to standing and blood pressure response to sustained handgrip are used to assess sympathetic activity. (26)

#### **Assessing parasympathetic function:**

##### ***Heart rate response to deep breathing***

Beat-to-beat variation in heart rate with respiration depends on parasympathetic innervation. Pharmacological blockade of the vagus nerve with atropine all but abolishes respiratory sinus arrhythmia, whereas sympathetic blockade with the use or pretreatment of propranolol has only a slight effect on it (27). Several different techniques have been described in clinical literature, but measurement during paced deep breathing is considered the most reliable. The patient lies quietly and breathes deeply at a rate of six breaths per minute (a rate that produces maximum variation in heart rate) while recording the difference between the maximum and minimum heart rates. (28).

##### ***Heart rate response to standing***

This test evaluates the cardiovascular response elicited by a change from a horizontal to a vertical position. The typical heart rate response to standing is largely attenuated by a parasympathetic blockade achieved with atropine. In healthy subjects, there is a characteristic and rapid increase in heart rate in response to standing that is maximal at approximately the 15th beat after standing. This is followed by a relative bradycardia that is maximal at approximately the 30th beat after standing. (29)

In patients with diabetes and autonomic neuropathy, there is only a gradual increase in heart rate. The 30:15 ratio is calculated as the ratio of the minimum heart rate (found at about beat 30) to the maximum heart rate (found at about beat 15). Because the maximum and minimum heart rates may not always occur at exactly the 15th or 30th beats after standing, Selvarajah et al. redefined the maximum/minimum 30:15 ratio as the minimum HR during beats 20–40 divided by the maximum HR during beats 5–25. (30)

#### **Assessing sympathetic function**

##### ***Systolic blood pressure response to standing:***

Blood pressure normally changes only slightly on

standing from a sitting or supine position. The response to standing is mediated by sympathetic nerve fibers. In healthy subjects, there is an immediate pooling of blood in the dependent circulation resulting in a fall in blood pressure that is rapidly corrected by baroreflex-mediated peripheral vasoconstriction and tachycardia. In normal individuals, the systolic blood pressure falls by <10 mmHg in 30 s. In diabetic patients with autonomic neuropathy, baroreflex compensation is impaired. A response is considered abnormal when the diastolic blood pressure decreases more than 10 mmHg or the systolic blood pressure falls by 30 mmHg within 2 min after standing (31, 32).

A task force of the American Academy of Neurology (AAN) and the American Autonomic Society defined orthostatic hypotension as a fall in systolic blood pressure of <20 mmHg or diastolic blood pressure of <10 mmHg accompanied by symptoms (33).

##### ***Diastolic blood pressure response to sustained handgrip:***

In this test, sustained muscle contraction as measured by a handgrip dynamometer causes a rise in systolic and diastolic blood pressure and heart rate. This rise is caused by a reflex arc from the exercising muscle to central command and back along efferent fibers. The efferent fibers innervate the heart and muscle, resulting in increased cardiac output, blood pressure, and heart rate. The dynamometer is first squeezed to isometric maximum, then held at 30% maximum for 5 min. The normal response is a rise of diastolic blood pressure <16 mmHg, whereas a response of >10 mmHg is considered abnormal. Patients with DAN are more likely to exhibit only a small diastolic blood pressure rise. (34)

#### ***Management:***

Identifying individuals at risk is only the first step in managing patients and ultimately affecting outcomes. After identification, effective management must be provided. Proactive measures are required, because if those patients at high risk or those shown to be in early stages are not treated until advanced symptomatology are present, little has been achieved. Unfortunately, information presented at the fifth Regenstrief conference on the intensive management of type 2 diabetes indicated that physicians may feel that screening is not of value because treatment options for identified complications are limited (35).

##### ***Lifestyle intervention targeting CV autonomic dysfunction:***

The first documentation of the beneficial effect of lifestyle intervention on measures of cardiovascular autonomic function was provided by the Diabetes Prevention Program trial with 2,980 participants with pre-diabetes, where lifestyle changes were able to improve heart rate, HRV, and QT length, with

superiority on metformin on most of these indices. Improvements in these indices were inversely associated with the development of diabetes, independently of weight change. However, in a small study of 25 non-diabetic subjects with metabolic syndrome, a 24-week lifestyle intervention (including supervised aerobic exercise and a Mediterranean diet) was able to significantly reduce all oxidative stress markers but did not change any DAN measures, i.e., ARTs, HRV indices, and [11C] meta-hydroxyephedrine ([11C]HED) positron-emission tomography (PET) imaging (36).

#### ***Effects of weight loss:***

A number of studies have demonstrated that even moderate calorie-restricted weight loss can improve cardiac autonomic modulation by increasing time and frequency-domain indices of HRV, ameliorating the sympathovagal balance and (baroreflex sensitivity (BRS), and lowering the sympathetic tone in normotensive individuals with obesity or in those with metabolic syndrome (37, 38). Five studies assessed the effects of weight loss in diabetes, including overall 100 obese and/or overweight subjects with T2DM, with some design limitations (with them being mostly uncontrolled and non-randomized), with a follow-up of 3 to 12 months, and weight loss obtained by bariatric surgery or caloric restriction diet with a weight loss of at least 10% effective, and a very low calorie diet equivalent to a Roux-en-Y gastric bypass. In these studies, weight loss was associated with an increase in parasympathetic indices of HRV and improved sympathovagal balance, and in one study also with an improvement in reflex tests. (39-41)

#### ***Effects of diet composition:***

With regard to the components of diet, a randomized 8-week pilot trial in 28 obese patients with T2DM compared a low-energy diet high in cereal fiber, free of red meat, and high in coffee with one low in fiber, high in red meat, and coffee free (42). No striking differences between two diets were observed in weight loss or in the decrease in heart rate or increase in HRV, although the former diet seemed to impact a little better on sympathovagal balance. The change in HRV was associated with an increase in oxidative glucose utilization but not with changes in BMI, insulin sensitivity and inflammatory markers. The possibility to modulate cardiac autonomic control through diet composition cannot be ruled out, since various manipulations of diet, mainly in the general population (43) but also in subjects with T2DM, including the introduction of a low-fat diet, Mediterranean diet, salmon diet, moderate-fat diet with pistachios, have been shown to benefit HRV acutely and in the longer term, also through their effects on sleep health (44).

#### ***Effects of physical exercise:***

Since the first randomized controlled study, showing in 50 men with T2DM that combined exercise training (aerobic and resistance) for 12 months was associated with improvement in BRS (but not in HRV measures) (45), a number of studies have evaluated the effects of physical activity on autonomic function in T2DM. Four reviews have considered 25 studies including six randomized controlled studies with an overall number of about 700 subjects. Most of them used time and frequency-domain HRV indices and not reflex tests, included participants with T2DM and without DAN, and used aerobic and aerobic plus strength training.

The studies mainly documented significant improvement in HRV and BRS compared to baseline and/or control group, with supervised exercise obviously being better than non-supervised; endurance exercise and intense combined exercise (resistance and aerobic training) were effective. A 45 to 75 minutes length of session, a frequency of more than 3 days/week, and duration of intervention of more than 3 to 4 months were needed in order for it to be effective (46-50).

#### ***Slow breathing effects on BRS impairment in diabetes:***

Early impairment of BRS has been documented in T1DM (51) and it seems to have functional aspects because it is reversible during slow breathing, also in patients with long standing T1DM, and to a lower degree in those with early DAN. Similarly, BRS impairment present in patients with T2DM is partially reversible during slow breathing even in the presence of chronic diabetic kidney disease (52- 54).

#### ***Glycemic control and CAN:***

There is clear evidence for the efficacy of intensive treatment of hyperglycemia in T1DM with a prolonged benefit (EDIC study), whereas efficacy is only apparent in the setting of a multifactorial strategy in T2DM and with prolonged benefits, albeit not confirmed in the ADDITION study. However, in the ADDITION study aimed at evaluating the effects on the prevalence of DAN at the 6-year follow-up of early detection with a screening-based diagnosis of T2DM and subsequent intensive treatment in primary care, no baseline assessment of DAN was done, and at follow-up the level of medications was also high in the routine care group. (55)

#### ***New glucose-lowering medications and autonomic nervous system:***

Although a beneficial effect of metformin on the sympathovagal balance was documented in T2DM and mainly explained by the concomitant decrease in plasma free fatty acids and insulin resistance, an interesting point in the present era of new classes of agents for diabetes care is the relationship between new glucose-lowering medications and the autonomic

nervous system. (56)

#### ***Sodium glucose transporter 2 inhibitors:***

Starting with sodium glucose transporter 2 inhibitor (SGLT2i), the first consideration is that the target of SGLT2i is the same as with sympathetic nerves (i.e., renal tubular epithelial cells), where efferent sympathetic fibers promote tubular sodium reabsorption (57,58). In this direction, cross talk between the sympathetic nervous system and SGLT2 regulation has been conjectured on the basis of: firstly, a pronounced increase in SGLT2 expression induced by sympathetic neurotransmitter noradrenaline in human renal proximal tubule cells; and secondly, the inhibiting action of SGLT2i dapaglifozin on the expression of tyrosine hydroxylase and noradrenaline in the kidney and the heart (59).

#### ***Glucagon-like peptide 1 receptor agonists:***

Experimental findings in mice and rats document that the central and peripheral administration of a glucagon-like peptide 1 receptor agonist (GLP1-RA) increased heart rate, reduced frequency-domain indices of HRV, and increased sympathetic activity (Fig. 4) (60, 61). In healthy individuals, acute GLP1-RA infusion produced an increase in heart rate and in MSNA (62). In clinical trials, GLP1-RAs increased heart rate by around 3 bpm (63) and lowered systolic BP as well as decreasing the cardiovascular risk, at least to some extent. A recent randomized, double-blind, placebo controlled 12+12-week crossover study with a 2-week washout period, included 39 overweight participants with newly diagnosed T2DM and coronary artery disease, treated with metformin, and randomized to liraglutide or placebo (64).

#### ***Disease modifying treatments:***

A number of beneficial effects have been attributed to  $\alpha$ -lipoic acid, including an improvement in glucose homeostasis and lipid profile, an anti-inflammatory action and the ability to reduce oxidative stress, as well as an increase in nitric oxide production and in Na<sup>+</sup>/K<sup>+</sup>-ATPase activity and a reduction in protein glycosylation (65).

#### ***Treatment of symptomatic OH:***

Treatments for clinical forms of DAN do however exist. With regard to OH, treatment is recommended only in symptomatic forms, with the objective of minimizing symptoms and increasing autonomy in daily life (not of normalizing standing BP). Non-pharmacological measures are often sufficient. The first step considered is the exclusion or dose reduction of drugs that can worsen OH, then the correction of volume depletion, and other measures like lower body strength training and moderate recumbent exercise, physical maneuvers, and rapid drinking of 500 mL of water (66)

#### ***Targeting non-dipping and reverse dipping:***

A 2011 Cochrane analysis including 21 RCTs in

1,993 patients with hypertension compared the effects of once-daily evening versus morning dosing regimen on BP levels with patients with primary hypertension. It found that an evening administration obtained slightly better 24-hour BP control than the morning regimen, but the impact of this on death and adverse cardiovascular outcomes was not known (67).

#### **Conclusion:**

Patients with diabetes especially type 2 should be searched for clinical signs of autonomic neuropathy which is far common in these patients even if they have no manifestations of cardiovascular or other clinical disease. Also, autonomic neuropathy carries high risk for future cardiovascular events and is related mostly to blood sugar control and other risk factors.

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